ANNALS OF INTERNAL MEDICINE

VOLUME 24 APRIL, 1946 NUMBER 4

MENINGOCOCCIC INFECTIONS IN AN ARMY STAGING AREA: ANALYSIS OF 63 CASES WITHOUT FATALITY FROM THE STANDPOINT OF EARLY DIAGNOSIS AND TREATMENT *

By A. ALLEN GOLDBLOOM, Lt. Col., M.C., A.U.S., F.A.C.P., EMANUEL H. NICKMAN, Major, M.C., A.U.S., and EDWARD E. P. SEIDMON, Major, M.C., A.U.S., *New Brunswick, N. J.*

WITHIN recent years medical opinion with regard to meningococcal infections and their treatment has undergone drastic revision. The early twentieth century concept that the meningococcus invades the meninges by way of the nasopharynx and cribriform plate was challenged in 1918 by Herrick [1] and later by others.[2, 3, 4] They expressed the belief that the infection enters the body through the nose and throat and then spreads to the blood stream which carries it to the various body tissues including the meninges where it becomes localized. However, if the resistance of the host is sufficiently great or if therapy is early and effective, the invasive process may be halted in the nasopharynx or in the blood stream and meningitis will not ensue. Therapy also has undergone a metamorphosis. Since the advent of the sulfonamides indications for the use of antimeningococcus serum and meningococcus antitoxin have gradually become more restricted because of the efficiency of chemotherapeutic agents in lowering mortality rates and decreasing the frequency of sequelae.

Two major problems, however, have not yet been completely solved, namely: (1) early diagnosis prior to localization of the organism in the meninges, especially in sporadic cases, and (2) optimum sulfonamide dosage. We have attempted in this paper to present findings which may be of assistance in the partial solution of these problems as well as to present an analysis of 63 cases of meningococcal infections treated at this institution.

* Received for publication Sept. 26, 1945.
From the Medical Service, Station Hospital, Camp Kilmer, New Jersey.

Copyright, 1946, by The American College of Physicians

Epidemiology and Vital Statistics

Medical statistics and literature have noted the increased incidence of meningococcal infections during wars when individuals are brought together for the first time in large groups. In World War I, 5839 cases were reported [5] among military personnel between April 1, 1917 and December 31, 1919.

The infection "was of relatively low incidence and was sporadic rather than epidemic in its occurrence in the Army, but its extremely high mortality made it of great importance as a cause of death in the United States forces. The case fatality varied in different camps from 9 to 63 per cent." [6] There were 2279 deaths, a mortality of 39 per cent.[5] During the years following World War I the incidence declined but again rose in 1943. In that year an increased number of cases was reported, especially among troops. The mortality, however, was much lower than in the First World War owing to the use of sulfonamides. Recent mortality estimates have varied between 3 per cent and 10 per cent.

In the period between July 4, 1942 and July 4, 1945, 63 cases of meningococcal infections were treated in the Station Hospital, Camp Kilmer, New Jersey. Sulfadiazine and its sodium salt were the sole therapeutic agents. No fatalities occurred in this consecutive series of cases. All patients recovered and were returned to duty. Within the period mentioned above slightly over one million seasoned troops were quartered and processed in this Camp preparatory to overseas movement. Transient troops made up over two-thirds of the cases seen. Not more than one case occurred in any one organization. The same was true of the small group of cases among permanent personnel of the Post. One case was seen in a white child, five years of age, the daughter of a soldier not stationed in this Camp. All cases were separated by a sufficiently wide interval of time to indicate that they were sporadic in character. Despite the fact that no epidemic per se existed on this Post, a greater number of cases was seen during 1942 and 1943 when a higher incidence of meningococcal infections existed among military personnel in the United States.

Racial distribution of cases included 54 (85.7 per cent) white patients and nine (14.3 per cent) colored patients.

Thirty-eight (60.3 per cent) patients came from urban and 25 (39.7 per cent) from rural communities and from these figures no conclusions can be drawn as to the significance of environment upon the incidence of meningococcal infections. Thomas [7] makes a similar observation.

Ages ranged from five to 54 years, the average being 26.6 years. The maximum number of cases (38) occurred in the age group of 20 to 30 years (60.3 per cent).[5, 8]

Nearly all of our patients (95.2 per cent) were seasoned soldiers with a minimum army service of five months and a maximum of nine years; 70.8 per cent fell into the service group of five months to one year and three

months. Only 4.8 per cent of soldiers had less than five months service. This incidence is in contrast to that found by Denny, Bausch and Turner [3] who reported that 82 per cent of their cases occurred in raw recruits with an average service of 2.7 months, and to that of Thomas [7] who noted that two-thirds of cases occurred in soldiers of less than three months service.

Clinical Considerations

From a study of the literature the erroneous impression is created that the diagnosis of meningococcal infections is comparatively clear-cut with a definite train of symptoms and signs which invariably include petechiae, stiff neck, Kernig's and various other neurological signs. This is true in epidemic periods when the course of the disease is so rapid and the nasopharyngeal and bacteremic stages are so evanescent that only the picture of a typical meningitis is present when the patient is first seen by the physician. However, in sporadic or chronic cases the above mentioned findings are not always present on admission and if present are frequently overshadowed by signs and symptoms referable to the skin, nasopharynx, blood stream, musculo-skeletal system and gastrointestinal tract. In over 50 per cent of our cases signs and symptoms of meningitis were absent on admission and findings suspicious of the following conditions were present: common respiratory infections, rheumatic fever, arthritis, appendicitis, acute exanthemata, obscure dermatological conditions, erythema multiforme, erythema nodosum, subacute bacterial endocarditis, undulant fever, psychosis, hysteria and acute alcoholic intoxication.

Early differential diagnosis is made the more difficult in sporadic cases because the percentage of positive blood cultures, the percentage of rash, the clarity of the symptomatology and the awareness of the physician of the possibility of meningococcal infection are less than in epidemics.

The function of our camp being the handling of large bodies of constantly moving troops, it may be seen that early and rapid diagnosis was of great importance to us, not only from the standpoint of the cure of the patient, but also for the purpose of treating contacts and carriers prophylactically to prevent them from acting as foci for the spread of the infection aboard crowded transports.

Accordingly, in order to facilitate early diagnosis and to better evaluate the relative importance of the signs and symptoms in meningococcic infections, we tabulated them as "early," occurring before or on admission to the hospital and "late," occurring subsequent to admission. The principal early findings in order of frequency were: nasopharyngitis, fever, headache, malaise, vomiting, myalgia and arthralgia and nuchal tenderness, splinting or rigidity. Of lesser frequency were: petechiae, nausea, irrationality, Kernig's sign, apathy or semi-coma, backache, coma, Brudzinski's sign and diaphoresis. A study of figure 1 makes evident the fact that the so-called classical findings do not necessarily occur early, but may develop later in the

disease and are of no help in establishing an early diagnosis. In our series no patient gave a history of contact and over 50 per cent were admitted to the hospital for conditions other than meningococcal infections, subsequent observation and study establishing the correct diagnosis. It is obvious from an analysis of figure 1 that, despite our desire to find significant early criteria, the early findings are not diagnostic of meningococcal infection but are common to a number of disease syndromes. However, it must be emphasized that in spite of their lack of specificity the frequency of their occurrence makes it imperative that one always consider meningococcal infection in the differential diagnosis when these findings are present.

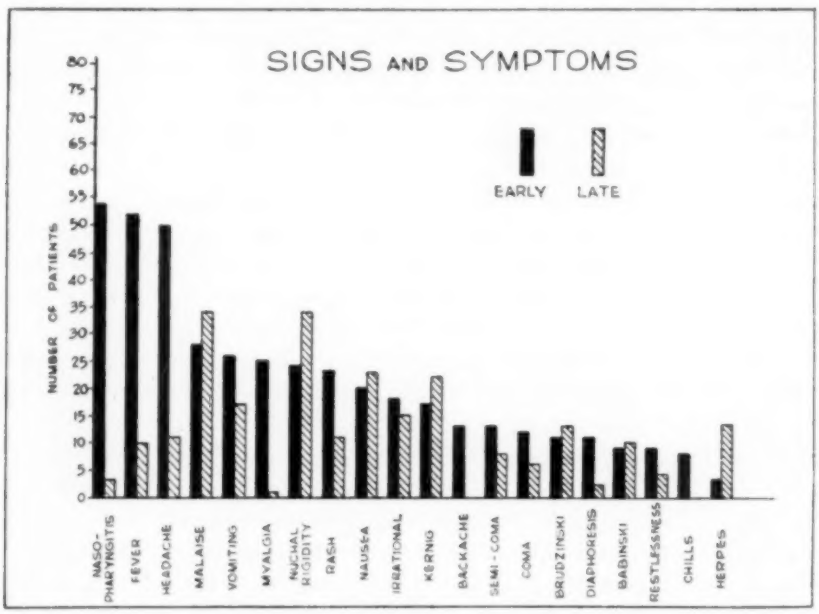


FIG. 1. Comparative frequency of early and late signs and symptoms in meningococcal infections.

Temperature, pulse and respirations were significant only insofar as they indicated the presence of an acute disease process. Temperatures averaged 102.4° F. with a maximum range of 98.6° to 105.2° F. Fever varied in type; in some it was septic and in others sustained low grade. The average pulse rate was 106.4 beats per minute, the highest recorded being 130 and the lowest 60. Respirations averaged 25.1 per minute. The highest rate was 40 and the lowest 16.

In this series we have classified our cases as mild (+), average (++), severe (+++) and fulminating (++++), depending upon the severity of the signs and symptoms, the rapidity of onset and the course of the disease. Eleven cases (17.5 per cent) were mild, 23 (36.5 per cent) were average, 23 (36.5 per cent) were severe and six (9.5 per cent) were fulminating or

moribund. The following typical case histories are illustrative of the above classified types:

1. Case history illustrative of the mild type of meningococcal infection:

A private first class was admitted to the hospital with a diagnosis of nasopharyngitis, having had cough, sore throat and mild headache for 24 hours. Upon admission he said that he did not feel ill except for a moderate generalized headache. Physical examination revealed a well nourished white male, 19 years of age, who did not appear to be very sick despite a temperature of 103.8°. No cutaneous rashes were present. His nasopharyngeal mucosa was red and edematous. Nuchal tenderness was present but forward motion of the head was only slightly impaired. The spinal fluid was cloudy, under moderate pressure and contained 4150 cells per cubic millimeter, 90 per cent of which were polymorphonuclear leukocytes. The spinal fluid sugar was 57.5 mg. per cent and the spinal fluid total protein was 100 mg. per cent. Culture of the fluid was positive for type I meningococcus. The blood culture showed no growth. Response to sulfadiazine therapy was prompt and uninterrupted, the patient becoming temperature-free on the third hospital day and symptom-free on the sixth hospital day. A total dosage of 52.5 grams of sulfadiazine was used. No complications or sequelae were encountered and the patient was discharged fully recovered after 44 days of hospitalization.

2. Case history illustrative of the average type of meningococcal infection:

A private first class, white male, age 40, was admitted with the complaints of mild sore throat, cough, nasal discharge, gradually increasing headache, weakness, chills, fever, somnolence, ringing in the ears and blurring of vision of three days' duration. Physical examination revealed an acutely ill soldier in a semi-stuporous state. No petechiae or other rashes were present. His throat was markedly reddened, his tongue furred and his breath fetid. Nuchal rigidity was severe, deep reflexes were hyperactive, and lateral nystagmus, Kernig's sign and ankle clonus were present. His spinal fluid was cloudy and under moderate pressure. Laboratory study gave the following information: spinal fluid—12,100 cells, 95 per cent polymorphonuclear leukocytes, total protein 750 mg. per cent, sugar 27.5 mg. per cent, culture positive for type I meningococcus; blood culture positive for meningococcus. Somnolence, nuchal rigidity, headache and hyperactive reflexes continued to be present for three days, but gradually decreased in severity under sulfadiazine therapy. On the fifth day his temperature was normal and on the sixth he was symptom free; however, he complained of weakness until the twenty-second day of hospitalization. The total sulfadiazine dosage was 48 grams. No complications or sequelae occurred. He returned to duty 46 days after admission to the hospital.

3. Case history illustrative of the severe type of meningococcal infection:

A second lieutenant, white male, age 26, was admitted in coma. A history subsequently obtained from him revealed that he had had a severe persistent headache and malaise for three days prior to hospitalization. On the day before admission he became very sleepy and developed pains in his neck, back and thighs. He apparently lost consciousness shortly thereafter as he remembered nothing of the period immediately preceding his entrance into the hospital nor for several days thereafter. The initial examination showed a well nourished white male, delirious and thrashing about in bed. His temperature was 102.6° F. Innumerable purpuric lesions varying from 0.2 to 2.5 centimeters in diameter were present upon the face, trunk and extremities. Several were noted upon the scrotum, conjunctivae and oral mucosa. The pharynx was moderately reddened. Neurological findings included: pronounced

nuchal rigidity, positive Kernig's sign, ankle clonus, lateral nystagmus and hypertonic tendon reflexes. The blood leukocyte count was 27,400 per cubic millimeter with 83 per cent polymorphonuclear cells. The spinal fluid was cloudy, under pressure and contained 15,100 white blood cells per cubic millimeter, 95 per cent of which were polymorphonuclear leukocytes. Spinal fluid showed a markedly elevated total protein, 800 mg. per cent, and moderately decreased sugar, 25 mg. per cent. The spinal fluid smear and culture as well as the blood culture demonstrated growth of gram negative diplococci which were identified as *Neisseria intracellularis*. For 24 hours the patient was wildly delirious and required physical restraint. There was some improvement on the following day, with partial return of consciousness and diminution of nuchal rigidity and rash; however, urinary incontinence, strabismus, lateral nystagmus and photophobia were still present. Consciousness was fully regained upon the third day but fever continued until the eighth day. Neurological signs consisting of weakness, areas of anesthesia and paresthesia of the lower extremities and slight pain in the left knee persisted until the seventeenth hospital day. After 57 days he was discharged to duty fully recovered. There were no sequelae.

4. Case history illustrative of the fulminating type of meningococcal infection:

A private, white, 20 years of age, was admitted with a diagnosis of nasopharyngitis. He had been ill for 12 hours with cough and nasal discharge. Immediately after admission he complained of severe headache and vomited. While his admission history was being taken he lapsed into coma and appeared to be in shock. His pulse rate was 118 per minute and his blood pressure 130 mm. Hg systolic and 80 mm. diastolic. No nuchal rigidity was present and Kernig's sign was equivocal. Petechiae were noted on the abdomen and back. Two hours later the patient became maniacal and had to be restrained. His skin was cold and bathed in a profuse sweat. Petechiae had increased in number and were visible all over the body. Nuchal rigidity was present; pupils were widely dilated and did not react to light; pulse was 126 per minute and of fair volume; blood pressure was 90 mm. Hg systolic and 60 mm. diastolic. The blood leukocyte count was 15,100, of which 97 per cent were polymorphonuclear leukocytes. The spinal fluid was cloudy, under pressure and contained 3,550 white blood cells, all of which were polymorphonuclear leukocytes. A spinal fluid smear showed the presence of intracellular diplococci. Growth of *Neisseria intracellularis* was subsequently demonstrated in the spinal fluid and blood cultures. A continuous intravenous infusion of salt solution in addition to sulfadiazine therapy was administered over a period of three days to which the patient responded slowly but progressively with gradual diminution of coma, shock and mania. Incontinence of urine and feces which was present during this period stopped on the third day. Temperature, pulse, respirations and blood pressure were normal on the fourth day. Although the patient's sensorium was not completely clear he was aware of time and place on the fifth day. Thereafter, recovery was rapid with abatement of all physical signs, nor had he any complaints except for occasional headaches, drowsiness and muscle soreness which were absent after the eighth day. He was discharged to duty on the forty-third day fully recovered.

Laboratory Data

Blood counts were usually indicative of an active infection. Most of the total white blood cell counts, 46 (73.0 per cent), fell between 10,000 and 25,000, the average being 16,030, the high 35,500 and the low 5,500. Although most of the counts showed a moderate leukocytosis, 11 (17.5 per

cent) were normal. It is important in the latter connection to keep the possibility of meningococcal infections in mind as normal or low white blood cell counts by no means exclude the diagnosis. Differential white blood cell counts invariably showed a relative leukocytosis. Polymorphonuclear leukocytes averaged 85.1 per cent, with a high of 99 per cent and a low of 63 per cent.

Neisseria intracellularis (meningococcus) was isolated in pure culture from the blood in 19 patients (30.2 per cent), from culture of the spinal fluid in 48 patients (76.2 per cent) and in stained spinal fluid smears in 24 patients (38.1 per cent). The type of meningococcus found was invariably type I.[9] In 11 cases no organism could be recovered. Of these 11 patients eight gave a history of having had sulfonamides prior to admission. Many reports have appeared in the medical literature to substantiate the fact that even small quantities of sulfonamides are sufficient to inhibit the growth of the meningococcus in spinal fluid as well as in vitro.[10, 11, 12] It is quite possible that such was the case in the above group. Three patients had not had sulfonamides as far as could be determined. In spite of negative cultures all of the 11 patients mentioned above had definite signs and symptoms of meningitis as well as large numbers of pus cells in their spinal fluids. The severity of these cases was: three +++, seven ++, and one +.

The average spinal fluid cell count, exclusive of seven cases of meningococcemia described below, was 9,915. The highest count obtained was 38,400 and the lowest was 50. The degree of clarity of the spinal fluid was roughly in proportion to the cell count, those with extremely high counts being purulent, those with moderate counts being cloudy and those with low counts being clear. The cells found in the differential cell count of the spinal fluid were predominantly polymorphonuclear leukocytes.

Spinal fluid in most cases revealed a moderate to marked depression of the sugar content, and the total protein content showed a moderate increase.

Meningococcemia

Seven cases of meningococcemia are included in this presentation. The clinical findings in these patients were at some variance with those of classical meningococcic meningitis. Positive cultures were obtained in 11 additional cases, but these, when first seen, had advanced beyond the septicemic phase and presented the picture of a typical meningitis and hence are not included as meningococcemias.

Meningococcemia may be extremely protean in its manifestations. The acute form, which is the type most commonly seen in epidemics, is of rapid onset with a spiking temperature curve, high pulse and respiratory rate, moderate to marked leukocytosis, profuse generalized petechial or purpuric rash and diaphoresis. In inter-epidemic periods this type occurs less frequently or may be subacute with similar symptoms but with a more gradual onset, more prolonged course and milder clinical manifestations. The chronic and chronic recurrent types are much more difficult to diagnose.

Their onset is slow and insidious with low grade persistent or undulant types of fever curve, malaise, vague aches and pains in the muscles and joints, swelling of the joints, a relatively small number of erythematous, purpuric or nodular skin lesions, and little or no elevation of the polymorphonuclear leukocytes of the blood. This picture may persist from several days to several months. It may clear spontaneously without treatment or may eventuate in meningitis.

One of our cases had acute meningococcemia with sudden onset 24 hours before admission, innumerable petechiae, nasopharyngeal engorgement, no neurological findings and normal spinal fluid. A second case, a white child five years of age, was ill for 12 hours before admission. She had sore throat, malaise, earache, stiff knees, nausea, vomiting, nuchal tenderness and a moderate number of petechiae. The spinal fluid was crystal clear and contained five cells. The spinal fluid revealed a reduction of the sugar to 5 mg. per cent and a normal protein content. Spinal fluid smear and culture were positive for meningococcus, type I. The blood culture was positive. This case represents an acute meningococcemia and an associated extremely early invasion of the meninges from the blood stream. There were three cases of chronic meningococcemia with ill defined symptoms varying in duration from four to 27 days. They showed evidence of upper respiratory infection, had tender or swollen joints, an erythematous or purpuric rash with from five to 10 lesions present, vague aches and pains, and tender nodules in the skin of the wrists, arms and neck. Two patients, ill for 10 days and 14 days respectively before hospitalization, were found to have chronic meningococcemia with signs and symptoms as in the above group, but eventually developing meningitis.

In addition to blood culture all cases in this group, as well as others suspected of having meningococcemia, were subjected to a diagnostic spinal puncture even in the absence of meningeal signs. This procedure enabled us to make a diagnosis by the isolation of the meningococcus in the stained spinal fluid smears of four patients who had no evidence of meningeal involvement many hours before the laboratory was able to report upon the blood cultures. In view of the above findings it is apparent that the organism is capable of early penetration of the meningeal barrier and may be identified in stained spinal fluid smears before the development of clinical reactions referable to the central nervous system and before marked alterations in the spinal fluid cell count and chemistry take place. We do not wish to infer that such findings are common. They are not. Nor do we believe that, in the absence of a positive spinal fluid smear and while waiting for the blood culture report, treatment should be delayed. In the presence of clinical signs of meningococcemia vigorous and early treatment must be instituted. In doubtful cases of meningococcemia, however, examination of spinal fluid smears, even in the absence of meningeal signs, may prove to be a more rapid means of identification of the organism than blood culture with the consequent saving of many hours before treatment is begun.

Therapy

Immediately following the diagnosis of a meningococcic infection it is our practice to administer the sodium salt of sulfadiazine intravenously to all patients even though they may be able to take the drug by mouth. In this manner we are able to obtain a high concentration of the drug in the blood stream more rapidly than would be secured by oral administration alone. In addition to the fact that intravenous is more rapid in its effect than oral medication, the former type of therapy is doubly important because of variability in the degree and rate of absorption of sulfonamide compounds from the gastrointestinal tract.[3, 13] It is a grave error to underestimate the seriousness of apparently mild meningococcal infections. All patients suffering from such infections are potentially seriously ill, not only from the standpoint of mortality but also because of resulting complications and sequelae.[3, 13] It is important, therefore, to obtain the optimum therapeutic level of the drug at the earliest possible moment regardless of the clinical appearance of the patient.

The standard therapeutic procedure for all cases of meningococcal infections as used on our service is as follows:

1. When a diagnosis of meningococcal infection is established, or in the presence of a suspicious spinal fluid prior to laboratory confirmation of the disease, the patient is given 0.5 per cent solution (5.0 gm.) of sodium sulfadiazine in 1000 c.c. of 5 per cent glucose in saline intravenously.

2. If the patient continues to remain in coma after the initial medication he is given 0.25 per cent solution (2.5 gm.) every six hours until he is able to take the drug by mouth.

3. As soon as oral medication is possible two grams of sulfadiazine are given by mouth every four hours for the remainder of the first 24 hour period following admission, then one gram every four hours until the temperature is normal. This is followed by a dosage of one gram three times daily until all acute symptoms disappear and for two additional days thereafter.

4. Sodium bicarbonate in the amount of 10 grains for every gram of sulfadiazine is given.[14]

5. Body fluid levels are maintained by the daily oral or intravenous administration of 3000 to 4000 c.c. of fluid. This amount insures a urinary output of at least 1200 c.c., sufficient to minimize the frequency of sulfacrystalluria.

The average total dosage of sulfadiazine per patient was 54.7 grams; the lowest was 27.0 grams and the highest 115 grams (see figure 2).

The average total oral sulfadiazine per patient was 48.0 grams; the lowest 17.0 grams and the highest 111.0 grams.

Fifty-four patients received sodium sulfadiazine intravenously, the average total dose being 7.2 grams. The lowest total dose was 4.0 grams and the highest 22.5.

Eleven patients were given sulfadiazine by gavage in an average total dose of 7.3 grams. The lowest total dose in this group was 4.0 grams while the highest was 23.0 grams. This mode of therapy was used only during a short period in 1942 and 1943. Its use thereafter was discontinued in favor of the more rapidly effective intravenous sodium sulfadiazine.

The medication given to the only child in our series is listed separately as her dosage and that of the adults are not comparable. She received 10.5 grams of sodium sulfadiazine intravenously and 11.5 grams of sulfadiazine orally, making a total dosage of 22.0 grams.

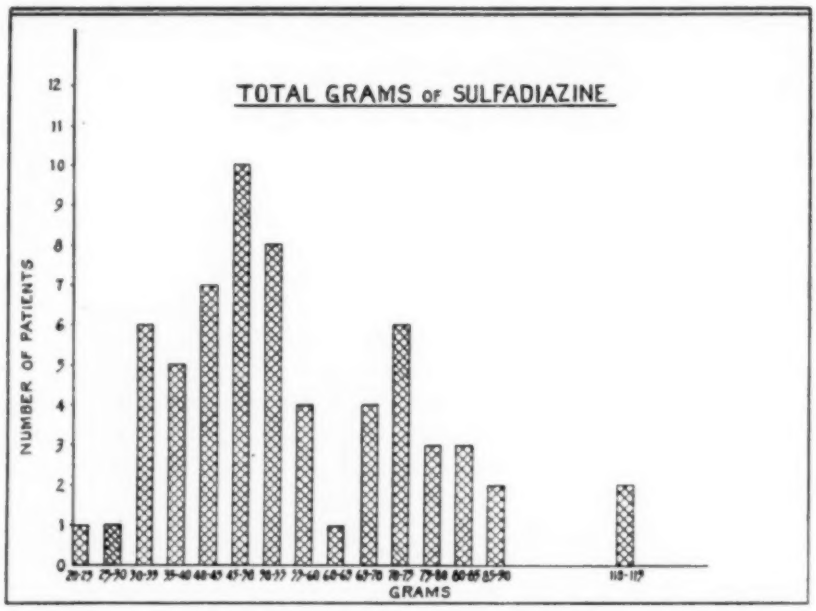


FIG. 2. Distribution of total sulfadiazine dosage in 63 patients treated for meningococcal infections.

Chemotherapy was administered to each patient for an average of 4.4 days before the temperature became normal. The longest recorded elevation was 12 days and the shortest was one day (see figure 3).

Medication was discontinued only when all signs and symptoms referable to the nervous system had subsided (see figure 3). We found it unnecessary to make cultures and sugar determinations of the spinal fluid before stopping treatment.[15] The clinical condition of the patient was a sufficiently reliable guide to make these procedures superfluous. No recrudescences occurred.

Patients became completely symptom-free after an average of 6.2 days. The high was 14 days and the low was three days.

Total days of chemotherapy were: average 7.6 days, high 14 days, low 3 days.

In no instance was other specific medication such as serum, antitoxin or penicillin used. Sulfadiazine and its sodium salt were the sole therapeutic agents. Supportive measures included paraldehyde for convulsive and violent patients, barbiturates for restlessness and caffeine sodium benzoate, which was helpful in some cases in reducing the severity of headaches. Opiates were not used.

We were unable to obtain figures for sulfadiazine blood levels which appeared to have any correlation with the therapeutic results obtained. In many cases where patients were receiving the same amount of drug the sulfa

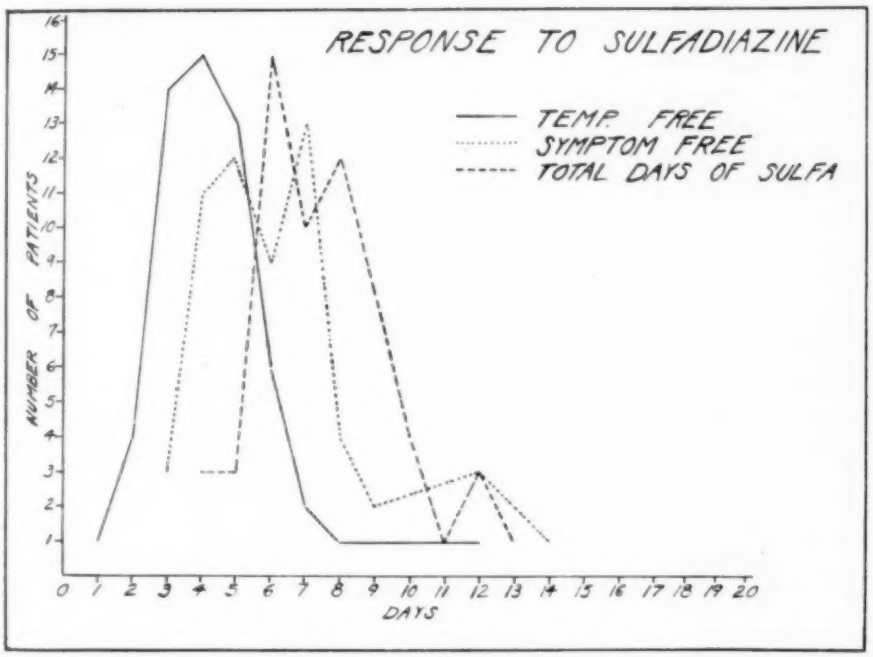


FIG. 3. Response to sulfadiazine in meningococcal infections: comparative duration of fever, symptoms and sulfadiazine therapy.

level was higher than 15 mg. per cent in some, whereas in others the sulfa level was lower than 5 mg. per cent. The therapeutic effect in those patients having a high level and in those having a low level was apparently the same, nor was there any time difference in the freedom from fever and symptoms in the high and low sulfa level groups.[16] It was noted, however, that patients receiving larger quantities of fluid frequently had lower sulfadiazine levels.[17]

Sulfadiazine blood levels were taken on each patient every second day during the first six days after treatment was begun. The average level attained was 8.7 mg. per cent, the lowest being 1.1 mg. per cent, and the highest 19.0 mg. per cent.

Convalescence and Rehabilitation

Despite the acute course of most meningococcal infections, the average patient becoming symptom-free in 6.2 days, it has been our practice to continue hospitalization for a much longer period. This insures the patient adequate convalescence and affords the opportunity of observing him for the possible development of late complications. At periodic intervals during his convalescence and immediately prior to discharge from the hospital he is given careful neurological, orthopedic and ophthalmologic examinations.

The average total hospital days per patient were 44.1. The longest period of hospitalization was 69 days, whereas the shortest was 15 days.

Following the acute phase of the illness each patient was started upon a program of mental and physical rehabilitation including arts and crafts, graduated physical exercises and light duties. At the time of discharge most patients had been completely rehabilitated and were ready for full military duty. Although the average number of hospital days in our group is similar to that of other Army installations, it is slightly higher than is reported by most civilian hospitals. However, the figures of the two groups are not comparable as most of our patients are completely rehabilitated during convalescence in the hospital and upon discharge are capable of performing full military duty, whereas patients discharged from civilian institutions more commonly are required to complete the terminal phase of their convalescence at home. The importance of such rehabilitation has been adequately demonstrated by the splendid results obtained in the reconditioning program of the Medical Department of the United States Army.[18, 19]

Complications

Table 1 tabulates the early and late complications encountered in our patients. The findings, in most instances, were mild and transitory in character. Neurological complications included: persistent headache, 3 cases; ptosis of the eyelids, 2 cases; low back pains, 2 cases; anesthesias and paresthesias, 1 case; diplopia and strabismus, 3 cases. Other complications encountered were: toxic myocarditis, 1 case; sinus bradycardia, 1 case; synovitis, 1 case; arthritis, 1 case; myositis, 1 case; and herpes simplex, 16 cases. It may be noted that herpes simplex was present in 25.4 per cent of all patients. However, it is apparent that it was of no diagnostic aid in early diagnosis as in 13 of the 16 cases the condition appeared from two to six days following admission to the hospital when the patients were already recovering. In only three instances was it present upon admission.

Toxic manifestations following the use of sulfadiazine included: sulfacrystalluria, 22 cases; microscopic hematuria, 5 cases; casts, 3 cases; kidney colic, 1 case; oliguria, 1 case; anemia, 1 case; rash, 2 cases; and cyanosis, 1 case. Urinary symptoms were troublesome in character in only two cases; namely, in one case each of oliguria and kidney colic, both of which responded readily to treatment. A moderate number of patients showed

TABLE I

Complications and Sequelae of Meningococcal Infections

Transitory Complications

Due to Disease

Headache—3
Ptosis of eyelids—2
Strabismus—2
Low back pain—2
Diplopia—1
Sinus bradycardia—1
Myocardial damage—1
Synovitis—1
Anesthesia and paresthesia—1
Transitory myositis trapezius muscle—1
Arthritis right hand—1
Herpes simplex—16

Due to Drug

Sulfa crystalluria—22
Microscopic hematuria—5
Hyaline casts—3
Rash—2
Kidney colic—1
Oliguria—1
Anemia—1
Cyanosis—1

Sequelae

Residual sciatica, left, mild—1
Sacro-lumbar pains—1
Headache—1
Post-meningitic syndrome, manifested by slow speech, moroseness and unfriendliness—1
Pain and anesthesia of right arm and right leg—1

crystalluria. In most of these, however, only a few crystals were present in the urine. This applies equally to the group with microscopic hematuria. Gross hematuria was not encountered. All of the above mentioned findings occurred during the acute state of the illness or in early convalescence. At the time of discharge from the hospital they had completely disappeared.

A small group of cases, five in number, had minimal residual findings at the termination of hospitalization. One patient had a mild post-meningitic syndrome manifested by slow speech, moroseness and unfriendliness. The other patients in this group had one of the following conditions: mild left sciatica, occasional lumbo-sacral pain, persistent dull headache and recurrent aches and anesthesias of the right arm and leg. All of the above five patients represent a group which delayed entering the hospital for from three to six days following the acute onset of signs and symptoms. It is our belief that these complications might have been prevented if sulfonamide therapy had been started early in the course of illness. This belief is substantiated by the fact that in 26 severe or fulminating cases and in 32 average or mild cases in which treatment was started promptly there were no sequelae.

DISCUSSION

Detection of the disease in its initial phases was of great concern to us because of our responsibility in certifying to the health of troops immediately prior to overseas movement. As many organizations were under our jurisdiction for only a few days before embarkation, any delay on our part in establishing a diagnosis might have resulted in the inclusion of contacts and carriers in the shipment. Crowding of men on transports being unavoidable, the presence of such foci would have been potentially dangerous. Ac-

cordingly, we attempted to differentiate between early and late signs in the hope that we would be able to find certain criteria which would assist in establishing a diagnosis before the disease had fully developed. It was found that the earliest signs and symptoms included nasopharyngitis, fever, headache, malaise, vomiting, myalgia and arthralgia. In themselves these findings were not significant but when they did occur a diagnosis of meningococcal infection was considered. Although many of the findings commonly associated with meningitis were present very early in the disease they were of much less frequent occurrence than those mentioned above.

Nuchal tenderness, splinting or rigidity and petechiae were the first definite leads to specific diagnosis. The other so-called classical signs in most cases became evident from one-half day to several days later.

Although over 50 per cent of our patients were admitted for other conditions with findings too meager to establish a correct diagnosis, the progress of the disease in others was so rapid as to present no great diagnostic problem. Not infrequently patients were admitted with a history of having been ill for less than 24 hours and upon examination presented a multiplicity of signs including coma, nuchal rigidity, petechiae, Kernig's and Brudzinski's signs, nystagmus, ankle clonus, diaphoresis and herpes.

Bacteriologic diagnosis was established by the isolation of the meningococcus either from the blood stream or from the spinal fluid. All cases suspected of having a meningococcal infection, including those in which meningococcemia alone was suspected, were subjected to a diagnostic spinal puncture. It has been observed by others [17] as well as ourselves that the organism may invade the meninges early and examination reveal a clear spinal fluid and minimal neurological signs. A stained spinal fluid smear in such cases not infrequently is found to be positive, thus establishing a diagnosis far in advance of confirmation by a positive blood culture with the resultant earlier institution of treatment.

Immediately following diagnosis sulfadiazine and its sodium salt were given in sufficiently large doses to secure a high concentration of the drug in the blood stream in the shortest possible period of time. It is our belief that the first 24 hours are the most important in the treatment of meningococcal infections and consequently more intensive therapy is required during that period for the following reasons:

1. The growth and proliferation of the organism is inhibited.
2. The tissue damage associated with the disease is checked, thus minimizing complications.
3. The necessity of giving large doses of sulfonamides on succeeding days is avoided.
4. The number of days of therapy is reduced.
5. Sulfa-fastness is prevented by giving adequate dosage in the initial phase of treatment.

Many papers have appeared in the medical literature with regard to optimum sulfonamide dosage in meningococcal infections. Harries [8] in 1942 reported 500 cases which were treated with sulfapyridine and sulfathiazole. His original total dosage was 28 gm.; however, after 250 cases had been treated the dosage was increased to approximately 38 gm. to diminish recurrences and septicemic complications. A small percentage of sequelae and a negligible percentage of toxic reactions from sulfa therapy were reported by this author. It is interesting to note that, although the total mortality was 8.6 per cent, in the age group of 15 to 25 years the mortality was less than 1 per cent. In its upper level this approximates the average age (26.6 years) of our own series as well as that of others [20] who report this as the most favorable age group from the standpoint of prognosis. In contrast to the low dosage mentioned above, Marangoni and D'Agati,[21] working with soldiers in favorable age groups, gave massive doses of sulfadiazine in amounts as high as 245 gm. and averaging 68 gm. Their mortality, exclusive of three patients who died within 12 hours following admission, was 3.1 per cent. Toxic reactions due to sulfonamides occurred in 28 per cent of their cases and included gross hematuria, kidney colic, anuria, oliguria and hemolytic anemia. Daniels, Solomon and Jaquette,[2] in a series of 112 cases with only one death, divided their patients into two therapeutic groups, one of which received an average total dosage of 87 gm. of sulfadiazine and the other 54 gm. They found no better therapeutic response from the use of the larger than from the smaller dose, and also found that the larger dose was more prone to cause kidney and other toxic sulfonamide manifestations not found in the group in which the smaller dose had been used. In our own series the average amount of drug employed (54.7 gm.) and the favorable results obtained closely resemble those of the small dose group of the investigators mentioned above [2] and is evidenced by the absence of mortality, the short febrile period, the short duration of clinical manifestations, the short period required for drug administration, the small number of toxic drug reactions and the small number of residual complications.

We feel that, in view of the above considerations, the optimum total dose of sulfadiazine in most cases of meningococcal infection lies between 50 and 60 gm.

Summary and Conclusions

1. Sixty-three consecutive cases of meningococcal infections were treated at an Army port of embarkation hospital during the period from July 4, 1942 to July 4, 1945. This group represents the total incidence in slightly over one million processed seasoned troops.

2. The disease was sporadic in occurrence. Diagnosis is frequently difficult and delayed in inter-epidemic periods. The value of early signs and symptoms in establishing a diagnosis is emphasized.

3. Therapy is most effective during the first 24 hours. All patients, regardless of their clinical appearance, must be considered seriously ill and treated accordingly. Intravenous therapy is the most rapid and satisfactory means of securing a therapeutic sulfonamide effect. Sodium sulfadiazine is recommended as the drug of choice for initial medication in all cases of meningococcal infection regardless of severity. Sulfadiazine and its sodium salt were the only chemotherapeutic drugs used. The average total dose per patient was 54.7 gm. No correlation was found between blood sulfadiazine concentrations and the clinical response obtained.

4. Complications due to the disease and toxic reactions following the use of sulfadiazine were negligible. All patients were returned to duty.

5. No fatalities occurred among the 63 cases reported.

BIBLIOGRAPHY

1. Herrick, W. W.: Early diagnosis and intravenous serum treatment of epidemic cerebrospinal meningitis, Jr. Am. Med. Assoc., 1918, lxxi, 612–617.
2. Daniels, W. B., Solomon, S., and Jaquette, W. A., Jr.: Meningococcic infection in soldiers, Jr. Am. Med. Assoc., 1943, cxxiii, 1–9.
3. Denny, E. R., Bausch, R. G., and Turner, M. A.: Meningococcal infection; meningococcal meningitis and septicemia, Am. Jr. Med. Sci., 1944, ccviii, 478–490.
4. Strong, P. S.: Recognition of meningococcic infections, Am. Jr. Med. Sci., 1943, ccvi, 561–566.
5. United States History of the World War. The Medical Department of the United States Army in the World War. Prepared under the direction of Maj. Gen. M. W. Ireland, The Surgeon General, Volume IX. Communicable and Other Diseases, by Lt. Col. Joseph F. Siler, Cerebrospinal Meningitis, 1928, chapter iv, 203–221.
6. Councell, C. E.: War and infectious disease, Pub. Health Rep., 1941, lvi, 547–573.
7. Thomas, H. M., Jr.: Meningococcic meningitis and septicemia; Report of outbreak in fourth service command during winter and spring of 1942–1943, Jr. Am. Med. Assoc., 1943, cxxiii, 264–272.
8. Harries, G. E.: Cerebrospinal fever; review of 500 cases treated by chemotherapy without intrathecal serum, Brit. Med. Jr., 1942, ii, 423–425.
9. Branham, S. E.: Meningococcus (*Neisseria intracellularis*), Bact. Rev., 1940, iv, 59–96.
10. Strauss, E., and Finland, N.: Bacteriostatic and bactericidal action of sulfadiazine in vitro on Gram-negative bacteria, Proc. Soc. Exper. Biol. and Med., 1941, xlvii, 432–434.
11. Neter, E.: Effect of sulfanilamide upon viability of meningococci in spinal fluid, Proc. Soc. Exper. Biol. and Med., 1938, xxxix, 84–86.
12. Levaditi, C., Girard, A., and Vaisman, A.: Chimiothérapie des infections expérimentales (gonocoque, méningocoque, pneumocoque et streptocoque) par la diacétyldioxydiphénylsulfone, Compt. rend. Soc. de biol., 1938, cxxvii, 19–21.
13. Smith, H. W., (Boston), Thomas, L., Dingle, J. H., and Finland, M.: Meningococcic infections; report of 43 cases of meningococcic meningitis and 8 cases of meningococcemia, Ann. Int. Med., 1944, xx, 12–32.
14. Fox, C. L., Jr., Jansen, O. J., Jr., and Mudge, G. H.: Prevention of renal obstruction during sulfadiazine therapy, Jr. Am. Med. Assoc., 1943, cxxi, 1147–1150.
15. Appelbaum, E., and Nelson, J.: Sulfadiazine and its sodium compound in treatment of meningococcic meningitis and meningococcemia, Am. Jr. Med. Sci., 1944, ccvii, 492–509.
16. Feldman, H. A., Sweet, L. K., and Dowling, H. F.: Sulfadiazine therapy of purulent meningitis, including its use in 24 consecutive patients with meningococcic meningitis, War Med., 1942, ii, 995–1007.

17. Hill, L. W., and Lever, H. S.: Meningococcic infection in army camp, Jr. Am. Med. Assoc., 1943, cxxiii, 9–13.
18. Rusk, H. A.: Convalescent care and rehabilitation in the army air forces, Med. Clin. North Am., 1945, xxix, 715–728.
19. Ranking, F. W., and Barton, W. E.: Present status of rehabilitation in the United States Army, Jr. Am. Med. Assoc., 1944, cxxv, 256–258.
20. Meyer, A. H.: Meningococcic meningitis: report on 165 cases, Ann. Int. Med., 1945, xxii, 543–545.
21. Marangoni, B. A., and D'Agati, V. C.: Treatment of 134 cases of meningococcic infection with massive doses of sulfadiazine, Am. Jr. Med. Sci., 1944, ccvii, 67–77.

MENINGOCOCCEMIA: A DESCRIPTION OF THE CLINICAL PICTURE AND A COMPARISON OF THE EFFICACY OF SULFADIAZINE AND PENICILLIN IN THE TREATMENT OF THIRTY CASES *

By J. Murray Kinsman, Lt. Col., M.C., A.U.S., F.A.C.P., and C. Anthony D'Alonzo, Capt., M.C., A.U.S.

Meningococcic infections are notoriously more prevalent in time of war, and during the past four years a relatively high incidence has been noted in army camps. This has afforded an unusual opportunity to study some of the less frequent forms of these infections. When the meningococcus localizes in the meninges there develops a clinical picture which presents no difficulty in diagnosis. If, however, the organism does not localize but remains active only in the circulating blood, the diagnosis is frequently overlooked. Although meningococcemia has been recognized with increasing frequency during the past few years, yet by 1943 there had been only 88 instances reported in the American and British literature.[1] Of these, the great majority were of the chronic variety in which the symptoms had persisted for a comparatively long period of time before the cause was recognized. Since that time cases of acute meningococcemia have been reported with increasing frequency, indicating that the diagnosis is being made much earlier in the disease. This form of the infection has been particularly common in army camps, and at this Post, in a period of 31 months out of the past three years, 33 proved cases were observed, and at least 29 cases were seen in which the diagnosis was not confirmed bacteriologically but in which the clinical picture was so characteristic that they can be considered as instances of meningococcemia. During the same period 111 patients with meningococcic meningitis were seen. Thus, at this Post, for every two cases of meningitis, there was approximately one case of meningococcemia without meningitis. This emphasizes the point that this form of infection is one of the most common types of disease produced by the meningococcus.

As a result of the profession's increasing awareness of this form of the disease, and because of the impetus given to its study by its comparatively high incidence in army camps, the clinical pattern of meningococcemia is emerging more distinct. It is now possible to make the diagnosis clinically without bacteriologic proof, with reasonable certainty, the most essential prerequisite being to think of its possibility.

This paper describes the clinical features of meningococcemia as seen in a group of cases in which the diagnosis was proved bacteriologically, and

* Received for publication October 5, 1945.
From the Medical Service, Regional Station Hospital, Fort Bragg, North Carolina.

compares this group with another group in which it was not confirmed; in both groups every patient was under the care and treatment of the same medical officer.

The therapeutic efficacy of sulfadiazine in meningococcemia is well established.[2, 3, 4, 5, 6] However, no reports of its treatment with penicillin have been seen. The present report compares the relative virtues of sulfadiazine and penicillin as therapeutic agents.

Clinical Material

Between February 1944 and June 1945, there were admitted to this hospital 61 patients with meningococcic infection, of whom 31 had meningitis, 15 had proved meningococcemia, and 15 had unconfirmed meningococcemia. The latter group of 30 cases of meningococcemia, confirmed and unconfirmed, constitutes the basis for this report. The age range was from 18 to 38 years, the average * being 24. One patient was a negro, the others white. The average duration of military service was three months. Nine of these cases occurred in January, four in February, three in March, three in April, two in May, four in June, three in July, one in September and one in October.

Proved Meningococcemia

Clinical Picture: There were prodromal symptoms in every instance (table 1): 11 patients had acute upper respiratory infections averaging one day in duration, and every patient had some fever, averaging one day in duration. In nearly every case, the acute illness was ushered in by chills, increase in fever, and headache. A rash developed in every patient but one. Two-thirds of the patients had nausea and vomiting, and three-quarters of them had joint pains. The admission temperature ranged from 99° to 104° and the highest temperature from 102° to 105°. The headache was conspicuously different from the generalized "splitting" or "bursting" type so characteristic of meningitis: it was throbbing in nature and usually frontal in distribution.

Although the characteristic eruption in meningococcic infections has generally been considered to be one of a hemorrhagic nature, yet in the cases of meningococcemia here reported, the typical lesion was a maculopapular one. Many of the macules took the form of pink plaques similar to the "rose spots" of typhoid fever. These varied in size from 2 or 3 millimeters in diameter to areas of 10 to 12 square centimeters. In approximately half of the patients, hemorrhagic lesions were also present in the form of petechiae or purpuric spots; frequently these petechiae appeared in the center of the macules. Several patients exhibited all varieties of the rash concomitantly. Many of the lesions were tender to pressure, especially the hemorrhagic forms. In some cases only a few indistinct and isolated spots were present,

* Throughout this paper wherever the word "average" is used, it is actually the median, which gives a more accurate picture of the actual situation than would the true average.

TABLE I

Pertinent clinical and laboratory data in 15 patients with acute meningococcemia, proved bacteriologically. The cases are divided into sulfadiazine-treated and penicillin-treated groups. Medians are used instead of means to express the "average"

Case No.	Age	Length of Service	Prodromata		Symptoms and Signs									Laboratory		Duration (After treatment was begun)	
			URI	Fever	URI	Chill	Fever	Head-ache	Nausea	Joint pain	Rash	Severity		Blood Cult.	Leuko-cyte Count	Fever	Rash
		Mos.	days	days								1	2	Type		hours	days
Sulfadiazine Treated																	
1	20	4	0	.5	0	x	x	x	x	x	x		x	1	19,000	12	2
2	21	15	12	10	0	x	x	x	x	x	x		x	1	14,000	12	4
3	19	0	14	1	x	x	x	x	x	0	x		x	1	13,000	12	3
4	24	3	1	.3	x	x	x	x	x	0	x	x		1	16,000	24	1
5	31	36	5	3	x	x	x	x	x	x	x		x	1	12,000	48	2
6	19	3	1	.5	x	x	x	x	0	x	x	x		1	13,000	24	2
Median or %	21	3.5	3	1	67%	100%	100%	100%	83%	67%	100%	33%	67%		13,500	18	2
Penicillin Treated																	
7	20	14	12	11	x	x	x	x	x	x	x	x		1	19,000	12	4
8	18	4	0	21	0	x	x	x	0	0	0		x	1	17,000	4	0
9	24	3	38	4	x	x	x	0	0	x	x		x	1	16,000	12	4
10	34	5	0	2	0	x	x	x	x	x	x		x	1	20,000	0	4
11	18	1	1	1	x	x	x	x	0	x	x	x		1	10,000	12	1
12	26	1	14	6	x	x	x	x	x	x	x	x		1	11,000	12	1
13	25	1	14	1	x	x	x	x	x	0	x		x	2A	13,000	9	2
14	24	2	0	1	x	x	x	x	0	x	x		x	1	25,000	10	1
15	22	3	1	.5	x	0	x	x	x	x	x	x		1	11,000	9	3
Median or %	24	3	1	1.5	78%	89%	100%	89%	66%	78%	89%	44%	56%		16,000	10	2
Entire Group																	
	22	3	1	1	73%	93%	100%	93%	67%	73%	93%	40%	60%		14,000	12	2

whereas in others the rash was widespread and coalescent. The most common locations were the shoulders, axillae, arms, chest, legs, abdomen and back, in the order named; the face was not involved in any of the patients. Buccal mucous membrane and conjunctival petechiae were seen in several instances.

Laboratory Findings: The leukocyte count varied from 10,000 to 25,000, averaging 14,000, and the percentage of neutrophiles from 80 per cent to 96 per cent.

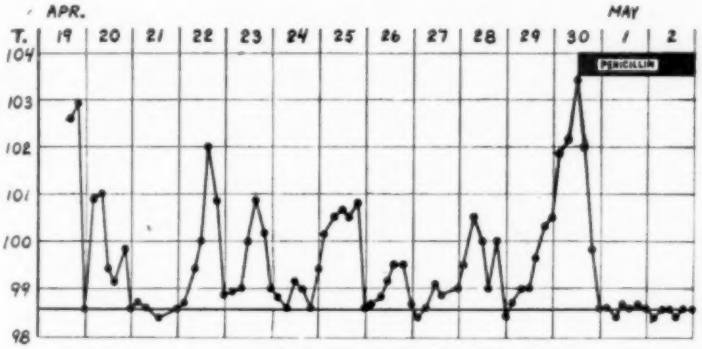


FIG. 1.

FIG. 2.

FIG. 1. The temperature chart of a patient with acute meningococcemia, treated with penicillin. This also illustrates one type of temperature curve seen in this disease. The diagnosis was not made until a rash appeared, on April 30. Blood cultures were later reported positive for the meningococcus.

FIG. 2. The temperature chart of a patient with acute meningococcemia, treated with sulfadiazine. The diagnosis was made clinically, shortly after admission, and it was later confirmed by a positive blood culture.

The meningococcus which was recovered from the blood was of Group 1 in 14 cases and of Group 2A in one.

The spinal fluid was examined in 10 patients, on six of whom three punctures were done for the purpose of assaying the fluid for penicillin.* In every instance the cell count, smear and culture were normal or negative.

UNCONFIRMED MENINGOCOCCEMIA

The clinical picture in the 15 cases of meningococcemia which were unconfirmed bacteriologically, was indistinguishable from that of the proved cases. The length of service, the duration of fever prior to the onset of the acute symptoms, the incidence of upper respiratory infections, chills, headache and nausea, and the leukocyte counts were all essentially the same (table 2). So too was the response to treatment as evidenced by the rapidity of disappearance of the fever and of the rash. The character and distribution of the rash were exactly the same as in the proved cases. The only differences between the two groups were the duration of the respiratory

* The results of these assays are being reported in a separate paper.

TABLE II

As for table 1 except that the diagnosis was not confirmed bacteriologically in any of the 15 patients.

Case No.	Age	Length of Service	Prodromata		Symptoms and Signs									Laboratory		Duration (After treatment was begun)	
			URI	Fever	URI	Chill	Fever	Head-ache	Nausea	Joint pain	Rash	Severity		Blood Cult.	Leuko-cyte Count	Fever	Rash
		Mos.	days	days								1	2	Type		hours	days
Sulfadiazine Treated																	
1	24	8	0	.3	x	x	x	x	x	x	x	x		0	21,000	12	1
2	38	4	9	2	x	x	x	x	x	0	x	x		0	9,000	20	2
3	25	8	0	2	0	0	x	x	x	0	x	x		0	15,000	28	1.5
4	20	3	1	14	x	x	x	x	0	0	x		x	0	10,000	24	2
5	19	3	2	.5	x	0	x	x	0	0	x	x		0	18,000	24	3
6	22	2	0	.5	0	x	x	x	0	0	x	x		0	17,000	96	2
Median or %	23	3.5	0.5	1.5	67%	67%	100%	100%	33%	17%	100%	83%	17%		16,000	24	2
Penicillin Treated																	
7	18	2	0	2	0	x	x	x	x	0	x	x		0	18,000	12	4
8	26	28	7	1	x	x	x	x	0	x	x	x		0	13,000	8	5
9	24	7	14	2	x	x	x	x	x	x	x		x	0	13,000	24	2
10	18	1	7	1	x	x	x	x	0	0	x	x		0	19,000	12	1
11	25	0	4	4	x	x	x	x	x	x	x		x	0	8,000	72	1
12	18	1	4	4	x	x	x	x	x	0	x	x		0	18,000	0	1
13	18	3	14	1	x	x	x	x	x	0	x		x	0	12,000	8	2
14	38	10	21	1	x	x	x	x	x	0	x	x		0	12,000	6	1
15	33	1	0	1	x	0	x	x	x	x	x		x	0	12,000	12	3
Median or %	24	2	7	1	89%	89%	100%	100%	78%	44%	100%	56%	44%		13,000	12	2
Entire Group																	
	24	3	4	1	80%	80%	100%	100%	60%	33%	100%	67%	33%		13,000	12	2

infection and the incidence of joint pains. The former can scarcely be considered a significant discrepancy, and evidence will be presented later in this paper to indicate that the lower incidence of joint pains in the unconfirmed cases should not introduce any element of doubt as to the correctness of the diagnosis. It is believed, therefore, that these 15 cases are truly instances of meningococcemia.

The spinal fluid was examined in nine of these patients and the cell count, smear and culture were normal or negative in every instance.

Treatment

For therapeutic purposes the 30 patients were divided into two groups without regard to the presence or absence of a positive blood culture. In nearly every case the diagnosis was made clinically and treatment was begun before the result of the blood culture was known. The 12 patients in Group 1 were treated with sulfadiazine and the 18 patients in Group 2 with penicillin. In the first 24 cases treatment was alternated between the two drugs, but the last six were treated with penicillin.

Dosage: (1) The initial dose of sulfadiazine was 4 grams, and was followed by 1 gram every four hours. This was continued until a normal temperature had been maintained for 48 hours, the average duration of therapy being four days, with a total dose of 27 grams. The concentration of the drug in the blood varied between 4 and 12 mg. per cent.

(2) In the first four patients, penicillin therapy was started with an intravenous dose of 40,000 units, followed in one hour by 40,000 units intramuscularly. The latter was repeated every three hours for 24 hours, after which 25,000 units were given intramuscularly every three hours for a total treatment period of five days. Since it became evident that that dosage was unnecessarily excessive, the next 13 patients received an initial dose of 25,000 units intravenously, followed by 25,000 units intramuscularly in one hour and thereafter every three hours. The total treatment period was five days except in one patient, in whom it was four days. One patient was treated with a sodium penicillin-beeswax-peanut oil mixture, containing 100,000 units per c.c., 1 c.c. being given intramuscularly, repeated 12 hours later, and then at 24 hour intervals for a total of six doses or 600,000 units.

Results: Every patient recovered. Since the mortality rate cannot, therefore, be used as a criterion of the comparative therapeutic efficacy of sulfadiazine and penicillin, other factors must be taken into consideration. Of these, the rapidity of disappearance of fever, of the symptoms and of the rash are of the most value in measuring therapeutic effect. In all of the 30 cases the symptoms usually disappeared within 24 hours after therapy was begun. The objective signs—the rate of disappearance of the fever and of the rash—are a more reliable index (tables 1 and 2). In the six proved cases treated with sulfadiazine the average time required for the temperature to reach normal was 18 hours whereas in the nine proved cases treated with penicillin it was 10 hours; in the unconfirmed group, the average time in the

six sulfadiazine-treated patients was 24 hours and in the nine penicillin-treated patients it was 12 hours. Grouping all the sulfadiazine-treated cases together, the average time was 24 hours, whereas for all the penicillin-treated cases it was 12 hours. Thus the duration of fever following penicillin therapy was 12 hours less than that following sulfadiazine therapy. In both groups the rash disappeared in two days on the average; occasionally the macular plaques would disappear within a matter of hours, though the petechial and purpuric lesions persisted longer. No complications followed either drug.

Two illustrative case reports follow, a representative one from each group:

Case Reports

Case 1. A 20 year old soldier was admitted to the hospital on April 19, 1944, with a history of a common cold beginning one day previously. On admission his chief complaints were headache, vomiting, and fever, and the temperature was 102.6° F., pulse 114, and respirations 24. Physical examination revealed nothing abnormal except a slight degree of pharyngeal injection. A leukocyte count was 10,500 with 80 per cent neutrophiles. The temperature receded to normal on April 21 (figure 1). However, the throbbing headache persisted, and on April 22 he again began to have a moderate fever, the temperature ranging from 98.6° to 102° F., continuing until April 29 when a few pink rose-colored spots appeared on his legs. During the morning of April 30 there was an increase in the headache. The temperature climbed to 103.4° F. On this day also, tender erythematous macules and plaques appeared in crops, still over the legs only. The leukocyte count had risen to 19,000 with 90 per cent neutrophiles. Later it was learned that blood cultures done on April 26, 27, 28, 29 and 30 all yielded the meningococcus Group 1. Neurological examination revealed normal findings. At no time had stiffness of the neck or Kernig's sign been present, but a spinal puncture was performed, the fluid being clear and colorless with normal dynamics; it contained no cells and the sugar content was 76 mg. per cent.

Penicillin was administered at 12 noon on this same day (April 30) using the smaller dosage schedule as outlined above. Spinal fluid was obtained eight and 24 hours later, the routine studies being normal and the penicillin assays negative. By 8 p.m. the temperature had dropped to 99.8° and to normal by midnight, remaining so for the duration of hospitalization. The rash disappeared four days after therapy was started. Penicillin had been administered over a five day period with a total dose of 1,025,000 units. Convalescence was rapid and recovery was complete. The patient was discharged from the hospital on May 13, 1944. (Note: This example is typical of the clinical picture of acute meningococcemia except for the unusual distribution of the rash.)

Case 2. A 24 year old white soldier was admitted to the hospital on March 18, 1944 at 3 p.m. Approximately one day before admission the patient developed an acute upper respiratory infection characterized mainly by soreness of the throat. About 10:45 a.m. on the day of admission he began to feel feverish, and this was followed by generalized muscle aching, shaking chills, dull, throbbing frontal headache and nausea.

On physical examination immediately prior to therapy the temperature was 102.3° F. and the pulse 96. The pharynx was slightly injected and a maculo-papular eruption was noted over the chest and forearms. Several of the lesions had very small petechial centers and these were tender to pressure. A leukocyte count was

16,000 with 86 per cent neutrophiles, and a blood culture later grew the meningococcus, Group 1.

At 6 p.m. on the day of admission therapy was started, consisting of 4 gm. of sulfadiazine by mouth. This was followed by 1 gm. every four hours. The temperature began dropping, and by 6 p.m. of the following day (March 19) it was normal and remained so for the duration of hospitalization (figure 2). By the time the temperature had reached normal the rash had disappeared. Convalescence followed and there were no sequelae. A total of 27 grams of sulfadiazine was administered over a four day period. The patient was discharged on April 1, 1944.

Discussion

When cases of meningococcemia are being seen only rarely there might be an understandable hesitation in making the diagnosis without bacteriological proof. However, when patients in whom the diagnosis has been proved are being seen rather frequently, as is the case in many army hospitals, one develops a high degree of alertness for the disease—a most important essential for its recognition. If one examines the two groups of cases herein reported—confirmed and unconfirmed—it is evident that there are no significant differences in the symptomatology, the physical findings, the clinical course or the response to treatment, between those patients with a positive blood culture and those with a negative one. Moreover, the clinical picture is so characteristic that when a patient is seen who presents all the typical features of the proved cases save only a positive blood culture, there can be little reasonable doubt as to the diagnosis. It should be emphasized that the characteristic rash is a sine qua non for making the diagnosis clinically.

It was not so many years ago that meningococcemia was considered a rarity. However, it has been reported much more frequently in recent years. The war has given an impetus to its study in that the incidence of meningococcic infections has shown a very great increase, and most of the larger series of cases reported since 1941 have been from army camps. One of the largest groups (32 cases) was reported by Daniels et al.[2] in 1943. Since their patients were seen at the same army hospital as those of the present report, it is of considerable interest to compare certain features of the disease in the two groups; the interest in the comparison is heightened by the fact that their patients were observed during the first four months of 1943, a period when the incidence was somewhat higher than normal, whereas the present authors' cases were seen over a 16 month period in 1944 and 1945 when the incidence was normal for the Post. Certain salient points for comparison between the two groups are set forth in table 3.

The similarity in general of the length of military service, the duration of the prodromal symptoms, the incidence of the different signs and symptoms, and the laboratory findings in the two groups is quite striking. In Daniels' patients, chills, headache and joint pains were not quite so common as in the authors', and more of the former were classified as mild in severity, but the differences are probably not of any great significance. Whereas in the

TABLE III

A comparison between the authors' 30 cases and 32 cases reported by Daniels, et al.[2] All figures are either medians or percentages.

No. of Cases	Age	Length of Service	Prodromata		Symptoms and Signs										Laboratory		Duration (After treatment was begun)	
			URI	Fever	URI	Chill	Fever	Head-ache	Nausea	Joint pain	Rash	Severity			Positive Blood Culture	Leuko-cyte Count	Fever	Rash
		Mos.	days	days	%	%	%	%	%	%	%	1	2	3	%		hours	days
Daniels et al.																		
Confirmed 18	22	2	1.5	1	78	61	100	78	72	28	100	61	33	6	100	18,250	24	4
Unconfirmed 14	21	1.5	6.5	1	78	29	100	78	43	50	100	93	7	0	0	16,400	24	3.5
Entire Group 32	22	2	3.5	1	78	47	100	78	59	38	100	75	22	3	56	17,600	24	4
Authors'																		
Confirmed 15	22	3	1	1	73	93	100	93	67	73	93	40	60	0	100	14,000	12	2
Unconfirmed 15	24	3	4	1	80	80	100	100	60	33	100	67	33	0	0	13,000	12	2
Entire Group 30	23	3	3	1	77	87	100	97	63	53	97	53	47	0	50	13,500	12	2

authors' cases joint pains were much more common in the proved cases than in the unconfirmed ones, in Daniels' cases the reverse was true, indicating that the absence of arthralgia cannot be regarded per se as a valid argument against the diagnosis of meningococcemia. It is significant, however, that the illness, as seen during a period when the incidence of the disease was greater than normal, did not appear to be of any greater severity than that during non-epidemic periods—and in fact appeared even milder.

Prior to the present war most of the cases of meningococcemia were of the chronic type, which lasted for weeks or months, and the diagnosis was frequently made only when meningitis developed. Since the war presented an opportunity to study comparatively large numbers of cases, the diagnosis has been made much earlier, and recent reports have dealt with the acute rather than the chronic variety of the infection. In one group of cases [7] reported in 1944, symptoms were present not longer than two weeks before the diagnosis was made. In the cases here reported the diagnosis was made within four days of onset, on the average, although in individual instances it required two to three weeks, and in one single case, 38 days to establish it. This point is worth calling attention to, to emphasize the fact that the diagnosis can and should be made very early in the great majority of cases.

There has been some objection on the part of some physicians to performing spinal punctures in cases of meningococcemia without meningitis, on the theory that the needle might introduce organisms into the otherwise sterile spinal canal. In the cases reported here no instance was encountered in which meningitis developed following spinal puncture. Of course treatment was begun immediately afterward or had been previously started. Although sulfadiazine could have aborted meningitis, yet experience at this hospital indicates that penicillin parenterally does not always sterilize the meninges. Hence it is concluded that the failure of meningitis to develop indicates that it is probable that spinal puncture is a safe procedure in cases of meningococcemia.

As judged by the symptoms, laboratory findings and clinical impression, there was no significant difference in severity between the sulfadiazine and the penicillin treated cases. For the purpose of comparing the effects of therapy the two groups were essentially identical in all respects.

There appears to be little difference between sulfadiazine and penicillin from the standpoint of the rapidity or the degree of response to therapy, although the temperature response to penicillin was somewhat more rapid by approximately a half day. The situation is comparable to that in pneumococcic pneumonia, wherein it has been demonstrated that sulfadiazine and penicillin are of almost exactly equal therapeutic value.[8] The decision as to which drug to employ depends, therefore, on other factors than the therapeutic effect: on the question as to whether the fear of possible toxic effects from sulfadiazine outweighs the nuisance of frequent and painful injections, at present necessary with penicillin; on the patient's ability to swallow and retain the sulfonamide; and on other factors such as sensitivity

of the individual to the sulfonamides, resistance of the meningococcus to the sulfonamides, etc. Should penicillin become available for general use in the form of a beeswax-peanut oil or other mixture wherein only one, or at the most, two injections a day are necessary, or should satisfactory preparations for oral use be developed, it is probable that its factor of safety over the sulfonamides will make it the drug of choice.

Summary and Conclusions

1. Within a 16 month period in 1944 and 1945, there were seen 31 soldiers with meningococcic meningitis; during the same period there were 30 patients in whom the diagnosis of meningococcemia without meningitis was made. Of these 30, the diagnosis was confirmed bacteriologically in 15 and was unconfirmed in 15. The average age was 23 and the average length of service was three months. Most of the cases occurred in the first six months of the calendar year.

2. A comparison is made between the 15 proved cases and the 15 unconfirmed ones. It is shown that except for the blood culture, the clinical picture in the two groups was essentially identical. The average duration of symptoms prior to diagnosis was less than four days; every patient had fever and a rash (one exception); most of them had an upper respiratory infection, chills, headache, and nausea; half of them had joint pains. The typical rash was maculo-papular rather than hemorrhagic, as is generally described.

3. A comparison is made between this series of 15 proved and 15 unconfirmed cases and a series of 18 proved and 14 unconfirmed cases seen at the same hospital in a four month period in 1943 and reported by other authors. There were no essential differences between the proved cases in each series nor between the unconfirmed cases. Moreover, in both series, no appreciable differences could be discovered between the proved and the unconfirmed cases. This lends further support to the conclusion that meningococcemia can and should be diagnosed clinically.

4. Spinal punctures were performed on 19 patients, and three times on six of them. In no instance did meningitis develop. Although the fact that treatment was already under way or was instituted shortly after could have prevented infection of the meninges, yet, since penicillin given parenterally does not always sterilize the meninges, it is concluded that spinal puncture in meningococcemia is a safe procedure.

5. Twelve of the patients were treated with sulfadiazine and 18 with penicillin. Therapeutic results were identical except that the temperature reached normal 12 hours earlier in the penicillin-treated group than in the sulfadiazine-treated group.

Addendum: Since the above paper was submitted, a patient has been seen who developed meningitis while she was under penicillin therapy for meningococcemia without meningitis. She recovered promptly when sulfadiazine was administered. This is the only instance of this occurrence to come to the attention of the authors, either from personal observation or from hearsay.

BIBLIOGRAPHY

1. Campbell, E. P.: Meningococcemia, Am. Jr. Med. Sci., 1943, ccvi, 566–575.
2. Daniels, W. B., Solomon S., and Jacquette, W. A., Jr.: Meningococcic infection in soldiers, Jr. Am. Med. Assoc., 1943, cxxiii, 1–9.
3. Smith, H. W., Thomas, L., Dingle, J. H., and Finland, M.: Meningococcic infections: Report of 43 cases of meningococcic meningitis and 8 cases of meningococcemia, Ann. Int. Med., 1944, xx, 12–32.
4. Bush, F. A., and Bailey, F. R.: The treatment of meningococcus infections with especial reference to the Waterhouse-Friderichsen syndrome, Ann. Int. Med., 1944, xx, 619–631.
5. Appelbaum, E., and Nelson, J.: Sulfadiazine and its sodium compound in treatment of meningococcic meningitis and meningococcemia, Am. Jr. Med. Sci., 1944, ccvii, 492–507.
6. Ochs, L., Jr., Weiss, T., and Peters, M.: Meningococcemia, Bull. of TBC, U. S. Army Med. Dept., 1944, lxxx, 86.
7. Potter, H. W., Reid, R. D., and Bronstein, L. H.: Meningococcemia without meningitis: A study made at the Station Hospital, Fort George Meade, Maryland, Ann. Int. Med., 1944, xxi, 200–214.
8. Kinsman, J. M., Daniels, W. B., Cohen, S., McCracken, J. P., D'Alonzo, C. A., Martin, S. P., and Kirby, W. M. M.: The treatment of pneumonia with sulfonamides and penicillin, Jr. Am. Med. Assoc., 1945, cxxviii, 1219–1224.

POST-DIPHTHERITIC POLYNEURITIS: A REPORT OF FIVE CASES WITH ALBUMINOCYTOLOGIC DISSOCIATION SIMULATING GUILLAIN-BARRÉ'S SYNDROME *

By MAHLON H. DELP, Lt. Colonel, M.C., A.U.S., GEORGE F. SUTHERLAND, Major, M.C., A.U.S., and EDWARD H. HASHINGER, Colonel, M.C., A.U.S., F.A.C.P., *Cleveland, Ohio*

IT seems highly probable that many cases of diphtheritic polyneuritis are being improperly designated as a primary neurological disease, and being erroneously catalogued variously as: infectious polyneuritis, radiculoneuronitis, or Guillain-Barré's syndrome. Review of the present literature and personal observation in retrospect adds confirmation to this belief. We are here reporting five cases manifesting several interesting features with one common finding—albumino-cytologic dissociation—in order to emphasize the ease with which they could have been dismissed in a like manner. In all respects these cases satisfy the original criteria set up by Guillain, Barré and Strohle [1] of polyneuritis, normal spinal fluid cell counts and increased cerebrospinal fluid protein, existing in patients with an ultimately favorable prognosis. In spite of the fact that these cases fall so clearly within this group, the diagnosis of preëxisting diphtheria can not be reasonably doubted.

Diphtheria rarely reaches epidemic proportion at the present time and the failure to recognize it is all the more likely since one is dealing with sporadic cases. Moreover, the neuritic symptoms frequently appear as a late complication after the initial infection has subsided undiagnosed. Signs, symptoms, bacteriology and the treatment for diphtheria have been known for years, but there seems to be a modern tendency to disregard the immediate and remote dangers of this serious disease. A high percentage of our children are well protected against diphtheria by active immunization, but a huge segment of the young adult population has no such defense. As with all communicable diseases, diphtheria has taken on new significance in war time.

The syndrome of polyradiculoneuritis with albumino-cytological dissociation of the spinal fluid was described by Guillain, Barré and Strohle in 1916. Their original report was based on the study of two cases. Since that time numerous reports of similar cases have appeared: for example, by Casamajor,[2] Bradford, Bashford and Wilson,[3] Kennedy,[4] Baker,[5] Jervis and Strassburger,[6] Shaskan,[7] and others. The syndrome has become well recognized and widely accepted. Correctly or incorrectly, it has been referred to as a disease entity probably resulting from infection with a neurotropic virus. The confusion attendant to acceptance of the syndrome as a specific entity

* Received for publication September 7, 1945.

is clearly shown by all writing upon the subject. Jervis and Strassburger describe a case presenting the characteristics of Guillain-Barré's syndrome yet they felt the pathological anatomy was definitely that of anterior poliomyelitis. De Jong [8] has questioned whether any of these polyneuritic syndromes belong to a single group of disorders or constitute a disease entity. Ederle [9] has raised similar doubts. That the nervous system sequelae of diphtheria be classed within the syndrome of "radiculoneuritis" with acellular hyperalbuminosis of the cerebrospinal fluid is quite acceptable. It is not acceptable that the possible primary etiology, infection with *C. diphtheriae*, go unrecognized. All such cases should be thoroughly investigated before being dismissed as a primary neurological disease. We believe the cause of good medicine is served by such insistence.

Case Reports

Case 1. This 24 year old white male was seen first on March 8, 1945 at which time he was complaining of weakness, difficulty on swallowing, and dermatitis. In July 1944, while serving in the Southwest Pacific, this patient developed a dermatitis which, although not disabling at the time, finally required hospitalization in November 1944. The dermatitis responded to treatment rather promptly. During this time, the patient had some mild difficulty with his eyes. He apparently was unable to accommodate properly. Approximately one month later a flareup of the original dermatitis, aggravated by secondary infection, required further hospitalization. On this admission the patient was treated with colloid baths and parenteral penicillin. Again the dermatitis responded to treatment and all except a few isolated lesions, including one on the left lower leg and several about the perineum, disappeared. On February 7, 1945 the patient, while still hospitalized, developed a very sore throat with formation of a left peritonsillar abscess. He received sulfonamides, the abscess drained spontaneously, and recovery seemed to be good. On February 18, 1945, 10 days after the onset of his acute tonsillitis, the patient noted difficulty on swallowing with regurgitation of liquid through his nose. Two days later weakness of his legs, mild shortness of breath, and a definite nasal voice developed. These symptoms were soon followed by tingling and numbness about the lips, the hands, the feet, and legs. He rapidly became very weak and barely able to sit up without aid. Such were the complaints at the time the patient was first seen here. In general appearance the patient seemed to be undernourished, very pale, sweating profusely and quite short of breath. On first examination the pulse rate was 120, blood pressure 96 mm. Hg systolic and 76 mm. diastolic, and an easily detectable gallop rhythm was present. In any other than a completely prone position, the patient exhibited profound vascular collapse and his blood pressure could not be determined. The neurological examination at that time revealed a nasal voice, complete paralysis of the right palate, partial paralysis of the left palate, failure of the right eye to converge, subjective difficulty in focusing, bilateral lower facial weakness, intact light touch sensation, pronounced hypalgesia over the face, extremities and trunk except for the ninth to twelfth thoracic dermatomes. There was marked weakness, marked fatigability and diffuse atrophy pronounced in the proximal girdle muscles. Tendon jerks in the upper extremities and ankle jerks were weakly active, knee jerks were absent, corneal and abdominal reflexes were normal as was the plantar reflex. The skin was quite clear except for some residual dark pigmentation. However, there was a healed lesion on the left lower leg resembling a healing ulcer approximately 1 cm. in diameter. Directly over the tip of the coccyx was an ulcer approximately 1 cm. in diameter and 1 cm. in depth. This lesion

was covered with a heavy crust of exudate and yielded cream-colored pus. The walls of the ulcer were covered with a gray tenacious membrane.

Smears and cultures from the throat and from the ulcer described above yielded numerous colonies of *Corynebacterium diphtheriae* of marked virulence for the guinea pig. The electrocardiogram showed a remarkably reduced voltage in all leads with a prolongation of QRS time characteristic of arborization type of intraventricular block. Other routine laboratory examinations, including blood counts, serologic reactions, routine blood chemical tests and urine examination, were normal with the exception of the white blood cell count. The initial white blood cell count was 16,200 with an essentially normal differential count. Examination of the cerebral spinal fluid showed a normal cell count with a spinal fluid protein of 215 mg. per cent.

With the diagnosis of post-diphtheritic paralysis and myocarditis thoroughly established, this patient was treated with 100,000 units of diphtheria antitoxin immediately. In addition to this, he was treated with penicillin in dosages of 10,000 units every two hours. Local applications of penicillin in aqueous solution to the cutaneous lesion were made frequently. Supportive therapy with adrenal cortical extract was also given during the critical state of his illness. Within a period of 10 days the myocardial lesion had largely subsided. The paralysis became more profound and the patient did not reach the peak of his disability until March 30, 1945. It was then noted that the palatal paralysis began slowly to subside. Subsequently a gradual return of the sensory and motor function of the extremities supervened. By July 1, 1945 patient was able to walk unaided. The cutaneous lesion, even with the topical application of penicillin in addition to the parenteral antitoxin, required about three weeks to heal. The lesion became negative for *C. diphtheriae*, however, within a matter of three days.

This case is of interest for several reasons: (1) It seems highly probable that this patient's initial lesion was one of cutaneous diphtheria and that his pharyngeal diphtheria was secondary. (2) The patient developed ocular palsies of transient character during one episode of dermatitis with mild improvement only to succumb to an overwhelming load of toxin from the combined cutaneous and pharyngeal lesions three and one half months later. (3) A severe myocarditis as shown by a gallop rhythm and extensive electrocardiographic disturbance was rendered more disturbing by the marked loss of peripheral vasomotor tone.

Case 2. This 19 year old male was first seen April 15, 1945. A casual from convalescent furlough, he presented himself on the third day of his illness complaining of a severe sore throat. Previous attempts to incise a peritonsillar abscess had resulted in no relief. The patient had the usual complaints of malaise, general muscular and body aches and fever. He was obviously acutely ill. His temperature on admission was 103° F., pulse 108, blood pressure 118 mm. Hg systolic and 80 mm. diastolic. He had a bilateral cervical adenopathy and marked swelling of the pharyngeal tissues on the left. There was no evidence of a definite membrane. Throat smears revealed a suspicious organism and when checked *C. diphtheriae* was isolated. This organism proved to have a high degree of virulence for the guinea pig. With identification of the organism on the fourth day of the patient's illness, he was given 60,000 units of diphtheria antitoxin in addition to the parenteral penicillin which he was already receiving. Improvement in the patient's general condition was prompt but on the tenth day of his illness he complained of difficulty on swallowing. He evidenced a nasal twang to his voice and had some failure in visual accommodation. Examination at this time showed obvious palatal paralysis bilaterally and a mild ocular palsy.

These findings remained fairly constant for the following days but by the twenty-eighth day of his illness the patient began to complain of paresthesias of the fingers, hands and arms, as well as of the feet and legs. No motor disability of the extremities developed.

Routine laboratory examination of this patient showed nothing unusual other than a white cell count of 15,200. The isolation of *C. diphtheriae* and proved virulence of this organism were as reported above. A preliminary examination of the spinal fluid showed a cell count of 2 with a spinal fluid protein of 57. The spinal fluid was again examined when the patient first complained of paresthesias in the extremities. Again the cell count was 2, and the spinal fluid protein was 92 mg. per cent.

Five weeks after the onset of paralysis, which had at no time become severe, the patient began to show steady improvement. The palatal paralysis first disappeared and was soon followed by progressive decrease in the paresthesias of the extremities. The only treatment given other than that mentioned above was in the form of a high caloric, high vitamin diet supplemented by the use of vitamin B complex parenterally.

This case represents a mild case of post-diphtheritic polyneuritis developing even though antitoxin was given. It is to be noted, however, that the antitoxin was given on the fourth day following the initial signs of infection. Here the spinal fluid did not show the characteristic albumino-cytologic dissociation when first examined. As the paralysis became more severe, the spinal fluid protein became elevated.

Case 3. This 31 year old white male was first seen May 25, 1945. His presenting complaint was one of weakness. A prisoner of war for a period of four months, he had been released on March 29, 1945 with these complaints. At the time the patient was first seen here he was actually slowly recovering. A recapitulation of the history shows that about February 15, while a prisoner, the patient developed a severe sore throat. Associated with the sore throat, the patient had a severe diarrhea. He was aware of the presence of a diphtheria epidemic in the camp in which he was held during the development of his own symptoms. His illness was reported but was not considered severe enough to warrant medication. No smears or cultures were taken. On March 29, 1945, the patient developed a left-sided pleurisy associated with pneumonia. On this occasion he was hospitalized and received treatment with sulfonamides. He promptly improved from his pulmonary complaints. Simultaneously with the onset of his pneumonia he began experiencing difficulty in swallowing, double vision, regurgitation of liquids through his nose, and tingling and numbness of all extremities. The patient had lost 60 pounds during his imprisonment and he considered the new symptoms only a part of his general debility. Upon being seen at this hospital the patient showed evidence of a great weight loss. He spoke with a nasal voice and evidenced marked weakness of the extremities and rather pronounced ataxia. Examination revealed a diminution in position sense, mild ocular palsy, loss of knee and ankle jerks, marked decrease in sensation in the extremities, particularly of the hands and feet. Examination of the cardiovascular system revealed nothing of importance. The blood pressure was 132 mm. Hg systolic and 80 mm. diastolic, pulse 80. The left pleura was considerably thickened and there was a small amount of fluid in the left pleural cavity. A diagnosis of post-diphtheritic paralysis was made on these findings and history. The routine laboratory examination showed nothing remarkable. The roentgenographic examination of the chest showed a moderately dense pleural thickening in the lower chest. No pulmonary disease could be demonstrated. Electrocardiogram was normal. The spinal fluid showed no white blood cells. The spinal fluid protein was 230 mg. The spinal fluid Wassermann reaction was negative.

No specific therapy was given this patient. He was placed on a high caloric, high vitamin diet supplemented with parenteral vitamin B complex. He made a rapid gain in weight and showed progressive diminution in all neurological symptoms and signs.

This patient developed a polyneuritis during a bout of pneumonia complicated by pleural effusion. It is important to note that this paralysis became apparent six weeks after the onset of a sore throat in a prisoner of war camp where diphtheria existed in epidemic form. No specific therapy was given at any stage in the illness.

Case 4. This 26 year old white male was first seen at this hospital on May 26, 1945. His presenting complaints were extreme weakness, tingling and numbness of the lips, arms, hands, feet and legs. On April 9, 1945, while this patient was a prisoner of war, he developed a severe sore throat. Two days later when seen by a physician a diagnosis of diphtheria was made. Some form of sulfonamide therapy (probably prontosil) was prescribed. Six days after the onset of the infection he was liberated as a prisoner. He then received 200,000 units of penicillin, sulfadiazine, and 40,000 units of diphtheria antitoxin. Cultures taken from throat smears on this date were positive for *C. diphtheriae*. The therapy was followed by prompt relief of all symptoms associated with his sore throat. Approximately five weeks after the onset of the patient's disease he noted diplopia and difficulty in accommodation. These symptoms were slowly progressive. By May 23, 1945 the patient developed a nasal voice, regurgitation of fluids through the nose and paresthesias of all extremities. These symptoms were becoming steadily more marked when the patient was first seen here. On examination the patient appeared to be in a fair nutritional state. He showed only mild difficulty in visual accommodation but did show rather marked weakness of all extremities. Taste sensation was largely lost. Two point touch discrimination was markedly disturbed. Vibratory and proprioceptive sensation was gone from the waist down. Sphincteric control was only partially adequate. The patient was quite unable to turn himself in bed, feed himself, or sit up. Routine physical findings were essentially normal. The cardiovascular system presented no changes. Blood pressure was 130 mm. Hg systolic and 82 mm. diastolic, pulse 80. The routine laboratory reports showed nothing remarkable. The electrocardiogram was normal. The cerebrospinal fluid showed a cell count of 1, a negative Wassermann reaction, and a protein of 127 mg. per cent. Four weeks later the protein had increased to 154 mg. per cent.

No specific therapy was given to this patient. During the first week of observation the patient continued to grow more completely disabled. He then began slowly to improve. He was given a high caloric, high vitamin diet supplemented with parenteral vitamin B complex. In addition he was given the usual physical therapy.

This case represents one in which the diagnosis of diphtheria was made early in the disease and was later proved by bacteriological studies. Treatment, however, was not made available until the ninth day of his illness. After five weeks of relative freedom from symptoms of any type, the patient began to show mild signs of neurological involvement with rapid progress to a state of complete disability.

Case 5. This 32 year old white male was first seen June 25, 1945, at which time he complained of weakness, tingling and numbness of feet, legs and hands. He actually made no mention of complaints except upon questioning, taking them as simply a part of his recent experiences. On December 22, 1944 this patient was taken

prisoner and on March 29, 1945 he was liberated. During this period the patient had an inadequate diet resulting in an estimated loss of 40 pounds. During February 1945 he became infested with lice and developed many indolent pustular skin lesions on the arms and legs. These lesions persisted. When liberated the patient was markedly exhausted, weak and exhibited besides his malnutrition many skin lesions and a low grade fever. He now recalls unusual weakness in the legs and describes paresthesias of the extremities, face and lips. He was placed on a high caloric and vitamin intake, given intravenous glucose and received 340,000 units of penicillin during the first three days of freedom. Sulfadiazine ointment was applied to the skin lesions. In general the patient improved rapidly but remained weak. This he did not consider unusual. He reported no unusual symptoms to his attending physicians. By May 20, 1945 his weakness and paresthesias of the extremities were quite distressing but sensory disturbances about the mouth had gone. The skin lesions were healing although leaving deep, pitted scars surrounded by a broad areola of brownish pigmented skin. On the date first seen here only one ulcer on the antero-lateral surface of the lower left leg remained. Examination of the patient revealed only a fair state of nutrition, with a weight of 135 pounds, whereas normal weight was about 160 pounds. Numerous healed scars of ulcers appeared on lower legs and arms. One ulcer on the left leg remained open. This lesion was shallow and had no membrane or unusual identifying characteristics. Routine physical findings were normal. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic. The heart and lungs were not unusual. Neurological findings were as follows: Cranial nerves normal, unsteady gait, increased tenderness of muscle masses of arms and legs. Poor coördination of finger to nose and heel to shin test. Triceps reflex very weak; all other tendon reflexes absent; no pathological reflexes. Vibratory sensation markedly diminished at ankles and slightly at wrists. Diminished sensitivity to pin point stimulation over distal portions of arms and legs. Light touch was recognized in all parts of body but was associated with paresthesia over distal parts of extremities. Routine laboratory findings were normal in all respects. Initial spinal fluid examination showed no cells and a protein of 67 mg. per cent. Subsequent examination four weeks later showed 4 cells and protein of 41.9 mg. per cent. Cultures from the open cutaneous lesion showed characteristic *C. diphtheriae,* which proved to be virulent for guinea pig. Progress was slow, but steady improvement continued on a high caloric, high vitamin diet supplemented by parenteral vitamin B complex. Topical penicillin to the ulcer was followed by prompt healing. At no time was the patient's disability great.

This represents a clear cut case of cutaneous diphtheria producing a polyneuritis in which the diagnosis of malnutrition and avitaminosis was not sufficient to account for all the neurological findings. The true nature of this feature was belatedly made only by bacteriological studies. Previously recognized and checked through several hands, these findings of polyneuritis had been repeatedly designated as due to avitaminosis.

In the past history of none of the patients was there evidence of immunity to diphtheria conferred either by the disease or active immunization. The Shick test on each at this late stage was negative. In cases 1, 2 and 4, the Shick test was invalidated by the recent administration of diphtheria antitoxin. Uniform bacteriological studies including stained smears, cultures and guinea pig inoculation for virulence determination, were carried out on cases 1, 2 and 5. The other cases presented no lesions lending themselves to such study.

Case	Spinal Fluid Cell Count	Spinal Fluid Protein
1	0	214
2	2	57
	2	92
3	0	230
4	1	127
5	1	67

TABLE SHOWING PROMINENT NEUROLOGICAL FINDINGS

	Case 1	Case 2	Case 3	Case 4	Case 5
Muscle weakness	+	0	+	+	+
Muscle tenderness	+	0	+	+	+
Ataxia	+	0	+	+	+
Loss of deep reflexes	+	+	+	+	+
Loss of superficial reflexes	+	0	+	+	+
Hypesthesia	+	+	+	+	+
Loss of vibration sense	+	+	+	+	+
Loss of light reflex	+	0	+	+	−
Loss of accommodation	+	+	+	+	−
Loss of convergence	+	0	+	+	−
Facial palsy	+	0	0	0	0
Loss of taste (anterior 2/3's)	+	0	+	+	−
Palatal paralysis	+	+	+	+	0
Hypesthesia pharynx	+	+	+	+	+
Paresthesias	+	+	+	+	+
Vasomotor paresis	+	0	+	0	0

DISCUSSION

A comparison of the pathology involved in post-diphtheritic paralysis and Guillain-Barré's syndrome is made very confusing both by a paucity of literature covering the first disease and the probable multiplicity of diseases reported as Guillain-Barré's syndrome. Wilson [10] has perhaps more thoroughly covered the nervous system complications of diphtheria than any other recent observer. He has stated: "The naked eye changes in the nervous system are confined to the hemiplegic forms in which petechial bleeding or some focal effusions may be remarked or thrombosed vessels." Wilson has said that endotoxins of diphtheria act directly on and cause acute changes in certain cells of the neuraxis. They also act directly on peripheral nerves apart from the cellular origins of the latter. He summarizes the pathologic lesions as follows: "a. Motoneurons and sensory protoneurons are damaged by a neurotoxin acting directly on parenchyma, and that while in general nerve fibers suffer first and most, other cases are distinguished by a primary attack on either nerve cells or motor end organs; b. Aside therefrom

any part of the neurons concerned will exhibit secondary reactions according to the rules of degeneration. Under the microscope, the dominant lesion is seen to be a neuritis, a parenchymatous degeneration of myelin sheaths of both motor and sensory fibers through their extent." Norris and his group [11] reported one case coming to autopsy which showed severe degenerative changes in the medulla and anterior horns of the spinal cord pointing to definite central nervous system involvement as well as peripheral damage.

The pathology of Guillain-Barré's syndrome is equally vague. It was Guillain-Barré's original contention that their patients had only the most favorable prognoses. Since the original description, a number of fatal cases have been reported. It is not at all clear how many varieties of disease might be represented in these reported pathological studies. Baker [5] has reported two fatal cases with pathological findings. He found changes consisting of perivascular foci of demyelinization scattered throughout the cerebral hemispheres, neuronal alterations within the cranial nerve nuclei, and patchy areas of myelin destruction within the peripheral nerves. Sabin and Aring [12] have reported three fatal cases with very careful and complete anatomical pathological studies. They found extensive visceral lesions consisting of focal degeneration and infiltration with mononuclear cells in the adrenals, liver and kidneys. Lesions in the heart consisted of interstitial infiltration with mononuclear and polymorphonuclear cells and, in one case, of necrosis of isolated muscle fibers and focal phlebitis. Zonal chromatolysis is described in the nerve cells of the spinal cord and medulla. In addition, degenerative changes were observed consisting of vacuolization and the appearance of many sharply outlined acidophilic bodies in the cytoplasm of some of the nerve cells in the abdominal sympathetic ganglia. After the study of these three cases, the writers expressed the belief that the existing data fit best the "hypothesis that infectious polyneuritis is caused by a toxin or toxins with affinities for the peripheral nerves and the viscera and elaborated by the microörganisms responsible for the infection of the respiratory tract which usually precedes the onset of nervous symptoms."

A comparative analysis of the clinical and clinico-pathological picture in post-diphtheritic paralysis and Guillain-Barré's syndrome is likewise not clear cut for the reader but less complex than that of the pathology. Case 4 which we have presented fits rather completely the classical signs, symptoms and clinical pathology of post-diphtheritic paralysis. There is the history of a sore throat with a membrane present and positive bacteriological findings clinching the diagnosis of diphtheria. The patient did not receive the known specific therapy until the ninth day of his illness, giving ample opportunity for the toxin to fix itself firmly in the nervous system tissue. After a delay of five weeks of comparative freedom from symptoms, there developed first ocular palsies, then palatal paralysis, to be followed soon by peripheral paresthesias, a gradual loss of all except superficial sensation and then a profound diminution in motor function. All of these signs and symp-

toms gradually disappeared over a period of weeks with a return to the normal. The spinal fluid findings were characteristically those of albumino-cytologic dissociation.

The clinical picture of Guillain-Barré's syndrome has been elaborated by Baker's [6] study in which he reported 33 patients. He has emphasized the following characteristics of this syndrome referred to as a "disease": 1. Sudden onset, occasionally preceded by a history of antecedent infection of the respiratory passages. 2. Absence of those findings suggestive of a septic or toxic reaction in spite of severe clinical symptoms. 3. Cell protein dissociation of the spinal fluid. 4. Radicular involvement. 5. Facial nerve palsy. 6. Absence of mental symptoms. 7. Favorable prognosis. This conforms very well with the original criteria of Guillain-Barré with some modification.

Elevation of the spinal fluid protein in post-diphtheritic paralysis has been observed and noted by Wilson,[10] Baker [5] and others, but the albumino-cytologic dissociation has not been emphasized. Since this has grown to be the most characteristic feature of the Guillain-Barré's syndrome, it is little wonder that so many cases are arbitrarily cited as examples with the finality of making a complete diagnosis. Ederle [9] has mentioned this finding in diphtheritic polyneuritis. He suggested that this placed it in the same category with "polyneuritis," "polyradiculomyelitis," Guillain-Barré's syndrome, etc. He further suggested this entire group be designated by the general descriptive term "serous radiculoneuromyelitis."

The above depicts the difficulty any student may have in attempting to compare either the clinical or the pathological findings in diphtheria of the nervous system and any other symptom complex at present falling into the group with which it is classified. This is especially true when it is noted time after time in case reports that the patient either shortly prior to the onset of neurological symptoms, or remotely so, had a respiratory infection or a sore throat.

Again referring to Wilson,[10] we find that he has recorded the frequency of neurological complications in diphtheria as varying with the observer from 8 to 66 per cent. Some variability of this incidence can also be attributed to the individual epidemic. The usual frequency is considered to be about 10 per cent. Norris et al.[11] report 18 cases of diphtheria occurring in the South Pacific 13 of which developed post infectional paralysis. This represents a very high incidence of paralysis, but is no doubt accounted for by the mild initial signs of infection and the late observation of the patients. Many cases showing mild ocular palsies and involvement of pharyngeal muscles surely go unobserved so that the exact incidence of nervous system damage is made still more difficult to determine.

The question naturally arises as to whether or not the five cases of polyneuritis observed here might have some unusual predisposition or susceptibility to nervous system damage by diphtheria toxin. This possibility was considered but not held likely. All patients had endured exposure, privation and additional disease. Four had been on inadequate diets for

weeks. Deficient vitamin intake was to be expected. Shulack and Peters [13] have recently reported a case showing spinal cord changes due to avitaminosis. The possibility of this patient having diphtheria previous to observation can not be dismissed. Failure to administer antitoxin early is apparently the important factor. Norris [11] and his associates found that antitoxin administered within four to 28 days of the onset of diphtheria did not prevent the paralysis. However, in those cases receiving antitoxin within three days, paralysis did not develop. This further confirms the belief that diphtheria toxin becomes fixed in nervous system tissue early after which it cannot be neutralized. In case 2 reported here, the patient received antitoxin five days after the onset of his illness. It did not prevent paralysis. Cases 1 and 4 received their antitoxin at much longer intervals after the initial appearance of diphtheria, hence no response was to be expected.

Cutaneous diphtheria as manifested by cases 1 and 5 is in itself of more than passing interest in war time. Cameron and Muir [14] have studied a group of 66 cases occurring in the Middle East. Saffron [15] has likewise reported such a case of recent date and reviewed the literature. Of particular import is the fact that Cameron and Muir found 12 cases of paralysis in the group of 66 cases observed. Unless the lesions are seen, examined, and an accurate bacteriologic examination made the true nature of the infection will go unrecognized. The broad areola of brown pigmentation surrounding the site of the original lesion we believe characteristic. It has color characteristics very similar to the residual pigmentation seen following a strongly positive Shick test. Two patients not included in this series but presenting signs of polyneuritis with elevated spinal fluid proteins had numerous lesions of like appearance on both legs. To us the diagnosis seems clear, but the lesions were healed and no bacteriologic examination could be made, hence they are not reported. The possibility that the resultant paralysis was improperly diagnosed as simple infective neuronitis or Guillain-Barré's syndrome is highly likely. *C. diphtheriae* finds cutaneous lesions and wounds excellent sites for remaining undetected until its toxin has attacked nervous system tissue.

Summary

1. Five cases of post-diphtheritic polyneuritis ("serous radiculoneuromyelitis") are presented.

2. A brief review of the literature covering the clinical picture, pathologic lesions and clinical pathology of the symptom complex variously known as "infective polyneuritis," "infectious polyneuronitis," Guillain-Barré's syndrome, has been made.

3. It seems probable that many cases reported as Guillain-Barré's syndrome, etc., are in reality cases of unrecognized diphtheria with late diffuse nervous system involvement.

4. Diphtheria should remain in the clinician's mind as a dangerous disease capable of high mortality if not recognized.

5. Cutaneous diphtheria is a serious lesion often resulting in prolonged disability because the toxin producing *C. diphtheriae* too frequently remains unrecognized while producing bizarre neurologic disease. The heavy areola of brown pigmentation surrounding the site of infection for months after healing is highly suggestive of a previous diphtheritic infection.

BIBLIOGRAPHY

1. Guillain, G., Barré, J., and Strohle, A.: Sur un syndrome de radiculonéurite avec hyperalbuminose du liquide cephalorachidien sans réaction cellulaire: Rémarques sur les caractères cliniques et graphiques des réflexes tendineux, Bull. et mém. Soc. méd. d. hôp. de Paris, 1916, xl, 1462.
2. Casamajor, L.: Acute ascending paralysis among troops, Arch. Neurol. and Psychiat., 1919, ii, 705.
3. Bradford, J. R., Bashford, E. F., and Wilson, J. A.: Acute infective polyneuritis, Quart. Jr. Med., 1918, xii, 88.
4. Kennedy, F.: Infective neuronitis, Arch. Neurol. and Psychiat., 1919, ii, 621.
5. Baker, A. B.: Guillain-Barré's disease (encephalomyelo-radiculitis). A review of 33 cases, Jr. Lancet, 1943, lxiii, 384–398.
6. Jervis, A. George, and Strassburger, Paul, J.: Guillain-Barré's syndrome ("infectious polyneuritis") and acute anterior poliomyelitis, Am. Jr. Dis. Child., 1943, lxv, 431–439.
7. Shaskan, Donald: Guillain-Barré's syndrome, an early diagnosis, Jr. Nerv. and Ment. Dis., 1943, xcvii, 280–282.
8. De Jong, Russell. N.: The Guillain Barré's syndrome, polyradiculoneuritis with albumino-cytologic dissociation, Arch. Neurol. and Psychiat., 1940, xliv, 1044–1068.
9. Ederle, W.: Serous radiculoneuromyelitis, Jr. Am. Med. Assoc., 1945, cxxviii, 549. Abstract from Deutsch. med. Wchnschr., 1943, lxix, 773.
10. Wilson, Kinnier, S. A.: Neurology, The Williams and Wilkins Company, Baltimore, 1940, i, 639.
11. Norris, Robert F., Kern, Richard A., Schenck, H. P., and Silcox, Louis E.: Diphtheria in the tropics. A report of 18 cases on a United States Naval Hospital Ship, U. S. Nav. Med. Bull., 1944, xlii, 518–524.
12. Aring, Charles D., and Sabin, Albert B.: Visceral lesions in infectious polyneuritis, Am. Jr. Path., 1941, xvii, 469–481.
13. Shulack, Norman R., and Peters, Michael: Spinal cord changes in avitaminosis, Bull. U. S. Army Med. Dept., 1945, lxxxviii, 118–120.
14. Cameron, J. D. S., and Muir, E. G.: Cutaneous diphtheria in Northern Palestine, Lancet, 1942, ii, 720–723.
15. Saffron, Morris H.: Cutaneous diphtheria as a military problem. Review of literature with a report of a case, Arch. Dermat. and Syph., 1945, li, 337–340.

TOXIC REACTIONS ACCOMPANYING SECOND COURSES OF SULFONAMIDES IN PATIENTS DEVELOPING TOXIC REACTIONS DURING A PREVIOUS COURSE *

By HARRY F. DOWLING, M.D., F.A.C.P., HAROLD L. HIRSH, M.D., and MARK H. LEPPER,† Capt., M.C., A.U.S., *Washington, D. C.*

THE sulfonamide drugs are so commonly administered at the present time that practically every person has received one of them on some occasion. Consequently, it is of importance to consider what will happen when these individuals receive sulfonamides a second time. Lyons and Balberor [1] reported that in patients who received a course of sulfathiazole without exhibiting any toxic effects "drug fever" was more likely to develop during a second course of sulfathiazole than in patients receiving an initial course of this drug. Two of us [2] have shown that this principle also holds for other sulfonamides, and, furthermore, that when patients are given a second course of a sulfonamide drug different from the one administered previously, the incidence of toxic reactions will be no greater than in patients receiving these drugs for the first time.

Of equal importance is the question of what can be expected to happen to the patient who receives a second course of a sulfonamide when a febrile reaction has occurred during the first course. In the present paper, we have analyzed the data on all the adult patients coming under our observation who have received more than one course of the sulfonamide drugs and who developed fever, dermatitis, conjunctivitis, or any combination of these reactions during the first course. We have grouped all three of these toxic phenomena together because it is the general consensus that they are all due to the same underlying mechanism, and because these various reactions often occurred interchangeably during different courses of sulfonamides, as we will show later.

Results. There were 78 adult patients altogether who developed fever, dermatitis, or conjunctivitis, or a combination of these reactions during the first course of sulfonamide therapy, and who received a second course of sulfonamides. As shown in table 1, the same sulfonamide was administered during both courses to 48 patients. Thirty-three, or 69 per cent, of these patients developed one of the toxic reactions under discussion during the second course. Thirty patients received a sulfonamide for the second course different from that given the first time. Only five (17 per cent) of these patients developed a toxic reaction. These differences are statistically significant.

* Received for publication August 2, 1945.

From the George Washington Medical Division, Gallinger Municipal Hospital and the Department of Medicine, George Washington University.

† Capt. Lepper's contribution to this study was made before he entered military service.

TABLE I

Patients Developing Fever, Dermatitis and/or Conjunctivitis during a Second Course of Sulfonamides after a Toxic Reaction during the First Course

Drug Received during First Course		Second Course: Reaction to Each Drug											
		Sulfanilamide		Sulfapyridine		Sulfathiazole		Sulfadiazine		Sulfamerazine		Totals	
		Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Sulfanilamide		0	2	0	1	1	1	—	—	—	—		
Sulfapyridine		—	—	2	0	—	—	0	1	—	—		
Sulfathiazole		—	—	0	2	13	5	0	11	—	—		
Sulfadiazine		—	—	—	—	0	4	7	3	1	1		
Sulfamerazine		—	—	—	—	2	3	1	1	11	5		
Patients receiving a second course of the same drug	No.											33	15
	%											69	31
Patients receiving different drugs	No.	—	—	0	3	3	8	1	13	1	1	5	25
	%											17	83

The particular sulfonamide drug used during the first or second course seemed to make no difference. The three drugs most frequently administered during two courses, sulfathiazole, sulfadiazine and sulfamerazine, produced toxic reactions during the second course in 69, 70, and 69 per cent, respectively, of the patients to whom they were administered.

It is also of interest that there was no significant difference in the frequency of reactions observed during the second course, when the reaction occurring in the initial course was composed of fever or dermatitis alone, as compared with the frequency of reactions observed when more than one toxic reaction was manifested during the first course. For instance, when fever was the sole toxic manifestation during the first course, a toxic reaction developed during the second course in 14 (78 per cent) of 18 patients receiving the same sulfonamide during both courses, and in one (17 per cent) of six patients receiving another sulfonamide during the second course. It will be seen that these percentages are very similar to those found for the entire series.

TABLE II

Type of Toxic Reaction Developing during Subsequent Courses of Sulfonamides Compared to the Type of Reaction Developing during the First Course

Toxic Reaction during First Course	Toxic Reactions during Second and Third Courses						
	Fever	Dermatitis	Conjunctivitis	Fever and Dermatitis	Fever and Conjunctivitis	Dermatitis and Conjunctivitis	Total
Fever	16	0	0	3	0	0	27
Dermatitis	1	5	1	0	0	0	
Conjunctivitis	0	0	1	0	0	0	
Fever and Dermatitis	5	0	0	7	0	1	16
Fever and Conjunctivitis	3	0	0	0	0	0	
	32			11			

In table 2 the types of toxic manifestations observed during the first course are compared with those observed during subsequent courses of sulfonamides. In general, the reaction tended to be the same during both courses, 29 patients showing the same reaction or combination of reactions, and 14 showing a different reaction or combination of reactions. Multiple reactions tended to occur more often during the first course (16 patients) than during subsequent courses (11 patients), but the differences were not statistically significant.

The length of the interval elapsing between the first and second courses had no bearing on the presence or absence of toxic reactions in the second course. In the case of one patient, fever began on the first day of the second course even though four months had elapsed between the courses of the sulfonamides. On the other hand, numerous patients failed to develop a toxic reaction during a second course, even though it began within a week after the end of the first course.

Nine patients received a third course of a sulfonamide after they had exhibited toxic manifestations to two previous courses of the same drug. In five of these patients, the third course produced toxic reactions. One of these five patients showed toxic reactions of increasing severity during the three courses, exhibiting fever with the first course, fever and pruritus with the second, and fever and a pruritic dermatitis with the third. Another one of the five patients, on the contrary, had fever and conjunctivitis during the first course, fever alone during the second, and only a low-grade fever during the third course. In another patient, similar phenomena of apparent desensitization appeared. This patient received only two courses of sulfadiazine and had fever and dermatitis both times. During the second course, however, the sulfadiazine was inadvertently continued after the appearance of the rash and fever, and these manifestations disappeared completely while the patient was still receiving the drug.

All of our attempts to prevent toxic reactions from recurring were unsuccessful. The measures which we used were: ascorbic acid, given between and during courses; aspirin or phenacetin, given just before and during courses; and small doses of the sulfonamide drugs themselves, given in one course lasting several days, or in several short courses.

Discussion

Park [3] tested nine patients who had developed fever, rash, or both, from the oral administration of a sulfonamide compound. All nine of them gave a similar reaction to a second course of the same drug whereas only three developed these toxic symptoms when given one of the other sulfonamides. It is apparent from his results and ours that the administration of a second course of a sulfonamide to a patient who developed fever, dermatitis or conjunctivitis during the first course of the same drug, is attended by a greater risk of toxic reactions. The risk is lessened considerably if a different sulfonamide is administered during each course, but it is still greater than we would expect in a patient who had experienced no toxic reaction to the first course. This can be shown by comparing the results obtained in the present study with those reported by two of us [2] on patients receiving second courses of sulfonamides, as we have done in table 3. This comparison also shows that the incidence of toxic reactions is less when a different sulfonamide is given than when the same sulfonamide is administered for both courses, whether a toxic reaction occurred during the first course or not. The present study, therefore, confirms the principle stated before,[2] that when a second course of sulfonamides must be given, the patient should receive a different sulfonamide from the one administered the first time.

Our findings also confirm the generally-held opinion that, in most instances, sensitivity to the sulfonamides is relatively specific for the individual drug, but that in some cases a group sensitivity develops which includes several or all of the sulfonamide drugs.

TABLE III

Frequency of Drug Fever, Dermatitis and/or Conjunctivitis during First or Second Courses of Sulfonamides

Reaction to First Course	Sulfonamides Administered during Second Course	Total of Patients	Patients Developing Toxic Reactions during Second Course	
			Number	Per Cent
No	Different drug	169	6	3.6
No	Same drug	144	16	11.1
Yes	Different drug	30	5	16.7
Yes	Same drug	48	33	68.8
	(Control series of persons receiving one course only)	737	37	5.0

SUMMARY AND CONCLUSIONS

1. Seventy-eight patients received a second course of a sulfonamide drug after showing fever, dermatitis or conjunctivitis during the first course. Among 48 patients to whom the same sulfonamide was given during both courses, 33, or 69 per cent, developed toxic manifestations, while only five, or 17 per cent, experienced a toxic reaction among the 30 patients who received a different sulfonamide during the two courses.

2. Neither the number of toxic reactions developing during the first course nor the particular sulfonamide drugs administered, nor the intervals elapsing between the two courses had any effect upon the appearance of toxic reactions during the second course.

3. Third courses were given to nine patients who had manifested toxic reactions to the first two courses of the same sulfonamide. Only five of these patients developed a toxic manifestation.

4. It is concluded that the patient who has previously experienced fever, dermatitis or conjunctivitis when receiving one of the sulfonamide drugs will run more risk of a similar reaction during a subsequent period of treatment with any of the sulfonamide drugs, even though a considerable interval of time may have elapsed between courses. If such a patient must be given a sulfonamide again, he should receive a different drug from the one used during the first course, and should be observed carefully for toxic reactions.

We wish to thank Dr. Lewis K. Sweet and the members of the Georgetown and George Washington Medical Divisions for their coöperation.

BIBLIOGRAPHY

1. LYONS, R. H., and BALBEROR, HARRY: Febrile reactions accompanying the readministration of sulfathiazole, Jr. Am. Med. Assoc., 1942, cxviii, 955–958.
2. DOWLING, H. F., and LEPPER, M. H.: "Drug fever" accompanying second courses of sulfathiazole, sulfadiazine and sulfapyridine, Am. Jr. Med. Sci., 1944, ccvii, 349–353.
3. PARK, R. G.: Sulphonamide allergy, Brit. Med. Jr., 1944, i, 781–782.

APATHETICAL RESPONSE TO HYPERTHYROIDISM; REPORT OF TWO CASES *

By Laura Hare, M.D., and James O. Ritchey, M.D., F.A.C.P.,
Indianapolis, Indiana

The problem of differential diagnosis, treatment, and prognosis of the various manifestations of thyroid disease remains a puzzling one in spite of intensive study directed toward its solution. Enumeration of but a few of the many conditions which may be simulated follows. First, the classic Graves' disease must be distinguished from the ophthalmopathic type of Means.[9] In this latter condition an extreme degree of exophthalmos is the outstanding symptom, set in a background of relatively mild toxicity, and treatment in the form of thyroidectomy tends to increase rather than to correct the deformity. Second, an intrathoracic goiter may be confused with a mediastinal Hodgkin's or other neoplasm.[3] Here roentgen examination and biopsy of an appropriate gland may aid in determining whether or not operation is indicated. Hypothyroidism and the pituitary type of myxedema [10] may be indistinguishable without the aid of laboratory tests. The hypercholesteremia, increased serum proteins, and menorrhagia, typical in the former and absent in the latter, help determine the proper medication. The administration of thyroid alone not only is ineffective but may precipitate an adverse reaction in those with pituitary dysfunction. Not the least of these problems is the distinction between hyperthyroidism and certain functional nervous disorders, since such factors as emotional instability, fatigability, palpitation, and loss of weight may exemplify both groups. It is only by familiarity with the typical picture of thyroid toxicity, so aptly described in the eighteenth century by Parry, that we may be alert to its unusual manifestations. Diagnostic confusion is particularly apt to arise among older individuals in whom the presenting symptoms may be auricular fibrillation and cardiac decompensation; a thyrocardiac or cardiotoxic state must be distinguished from a purely organic cardiac disease. As far back as 1923 this relationship was pointed out by Hamilton [2] in his report of a series of 22 cases treated at the Lahey Clinic. These individuals had in common an enlarged heart, auricular fibrillation, congestive heart failure, and increased basal metabolic rates; they were all treated surgically with good results. Subsequently many such instances have been described [1, 4, 5, 6, 7, 8] wherein the clinical evidence of profound cardiac disturbance, usually in women past middle age, overshadowed the hidden factor of hyperthyroidism. The onset is typically gradual, the gland is firm and equivocally enlarged, the spectacular symptoms of toxicity may be wholly or in part replaced by a deceptive mask of mental and physical inertia.

* Received for publication September 18, 1945.

The cases to be reviewed suggest an even more exaggerated state of muscular weakness, apathy, and debilitation, yet at the same time are devoid of the cardiac manifestations.

Case Reports

Case 1. M. M., a 55 year old housewife, was admitted to the Robert Long Hospital on September 19, 1944, because of choking spells, pain in the lower extremities, loss of appetite, and prostration. For two years her usual activities had been curtailed by dyspnea, palpitation, and emotional instability. Anorexia and weight loss developed proportionately, and more recently her ankles had been swelling in the evenings. Finally she had become bedfast two days before hospitalization.

Physical Examination: The patient was poorly nourished, weighing just less than 100 pounds, lay quietly in bed, and evinced no interest in her surroundings. There was no dissipation of energies, no expression of alacrity in her eyes. She was too weak to change her position in bed without help and the mere exertion of talking was accomplished with apparent effort. Her skin, particularly pigmented about the eyes, was soft in texture, warm, and moist. The temperature was 99° F., pulse 100, and regular. Blood pressure was 145 mm. Hg systolic and 70 mm. diastolic. A moderately enlarged, firm, nodular goiter was palpated. The precordium was active and the heart normal in size. A systolic murmur and an accentuated pulmonic second sound were present. The lung bases were clear and there was no peripheral edema.

Laboratory Data: Urine analysis gave a normal result. The hemoglobin content of the blood was 13 gm., and the white cell count was 5,000 with a normal differential. The Mazzini serologic reaction was negative. The sedimentation rate (Wintrobe) was 28 mm. in one hour and the blood non-protein nitrogen was 33 mg. per cent. Basal metabolic rates were + 76, + 50 and + 54.

Course in the Hospital: She was treated with bed rest, vitamin B complex, and thiouracil 0.2 gm. three times daily. She was unable to feed herself the first few days but as her appetite improved she made gratifying though erratic progress; within a month her intake averaged above 2400 calories and she began to gain weight after an initial loss of four pounds. Her white count was checked regularly and at no time fell below the normal value. By the latter part of October she had become increasingly more stable, her basal metabolic rate was + 24, and she was referred to surgery on the last day of October for a bilateral subtotal thyroidectomy. She was discharged from the hospital on November 8 following a satisfactory postoperative course.

Pathological report: Degenerating nodular goiter showing calcification.

A follow-up check on her condition five months and seven months later revealed a weight gain and increase in strength so that she was able to do her housework with ease. There was no residuum of her previous apathy.

Case 2. L. M., a 42 year old housewife, was sent to our hospital on September 17, 1942 with a tentative diagnosis of malignancy of the stomach, suggested by her complaints of inability to eat because of nausea and epigastric discomfort, malnutrition, and extreme weakness. She had begun to lose weight three years previously, at which time she weighed 189 pounds, but her local doctor was not consulted until April, 1942. She became bedfast in June because of nausea and vomiting and pain in her stomach and upon further questioning it was learned she had suffered severe financial reverses about this time. There was no record of hematemesis or melena but she had had recurrent episodes of diarrhea. In July she became jaundiced and had remained so. Her loss of weight and strength to the point of cachexia became alarming during the late summer. Nothing in her past history threw light on her present illness; she was the mother of eight children and had passed through an artificial postoperative menopause 13 years previously.

Physical examination revealed an emaciated individual weighing about 70 pounds. The temperature was 99.6° F., pulse 130, and blood pressure 150 mm. Hg systolic and 95 mm. diastolic. Her demeanor was that of utter lassitude and resignation, entirely devoid of every vestige of spontaneous animation. This mask was found to be vulnerable, however, to any references made to her financial losses, the apparent precipitating factor in her change for the worse early in the summer. To recall this to her mind was to initiate paroxysms of insuppressible weeping. Her skin had an icteric tint, was soft and warm, but showed evidence of dehydration. There was a minimal bilateral nodular enlargement of the thyroid. The heart size was not increased, the beats were regular and thrusting in nature, and a systolic murmur could be heard at the apex and along the left sternal border. Examination of the lungs was essentially normal. Palpation of the upper abdomen revealed tenderness and a questionable small epigastric mass. The liver border could be readily felt.

Laboratory Data: The urine was negative except for a faint trace of albumin. The white cell count of the blood was 7,600 with a normal differential. Hemoglobin was 13 gm., and Mazzini reaction was negative. Blood chemistry: direct van den Bergh positive; indirect 1.4 mg. of bilirubin; icteric index 29; serum cholesterol 165 mg. per cent; and non-protein nitrogen 25 mg. per cent. A glucose tolerance test was essentially normal and three basal metabolic rates were + 95, + 100 and + 100. Roentgen examinations of the chest, gall-bladder, stomach, and bowel revealed no demonstrable deformity.

Course in the Hospital: She was placed on a high caloric diet, vitamin B complex, and Lugol's solution, 10 drops three times a day. In spite of bed rest her pulse continued to fluctuate between 90 and 130. During the ensuing weeks her appetite and food tolerance increased so that she was averaging between 3900 and 4900 calories per day and her weight rose to 96 pounds. It was decided to operate upon her in two stages and accordingly the right lobe was removed on November 6. She returned the latter part of December for removal of the other lobe on January 6, 1943.

Pathological report: Partially involuted exophthalmic type of goiter with a few areas of nodular formation.

She was seen again in our out-patient department two years later in apparent excellent health. She weighed 171 pounds, had a good appetite, was working hard, and made no complaints.

Summary

These cases exemplify yet another clinical response to thyroid toxicity. A distressing picture of extreme apathy, disinterest, and resignation, associated with loss of weight and weakness to the point of prostration, made necessary a differential diagnosis from Simmonds' disease, advanced tuberculosis, Addisonianism, anorexia nervosa, and acute depressive psychosis. There was a profound masking of their fundamental problem of hyperthyroidism, but their satisfactory response to presurgical medical therapy, both in the form of Lugol's solution and thiouracil, and finally to thyroidectomy, corroborated the diagnoses.

BIBLIOGRAPHY

1. Averbuck, S. H.: Masked hyperthyroidism as a cause of heart disease, Ann. Int. Med., 1942, xvi, 1011–1018.
2. Hamilton, B. E.: Thyroidism complicated by heart failure, Jr. Am. Med. Assoc., 1923, lxxx, 1771–1774.

3. HERTZLER, A. E.: Diseases of the thyroid gland, 1942, Paul B. Hoeber, Inc. (Harper & Bros.), New York, pp. 470–487.
4. LAHEY, F. H.: Apathetic thyroidism, Ann. Surg., 1931, xciii, 1026–1030.
5. LAHEY, F. H.: Activated and apathetic hyperthyroidism, South. Surg., 1932, i, 36–38.
6. LAHEY, F. H., and HAMILTON, B. E.: Thyrocardiacs; their diagnostic difficulties: their surgical treatment, Surg., Gynec. and Obst., 1924, xxxix, 10–14.
7. LEVINE, S. A., and STURGIS, C. C.: Hyperthyroidism masked as heart disease, Boston Med. and Surg. Jr., 1924, cxc, 233–237.
8. LIKOFF, W. B., and LEVINE, S. A.: Thyrotoxicosis as the sole cause of heart failure, Am. Jr. Med. Sci., 1943, ccvi, 425–434.
9. MEANS, J. H.: The nature of Graves' disease with special reference to its ophthalmic component, Am. Jr. Med. Sci., 1944, ccvii, 1–19.
10. MEANS, J. H., HERTZ, S., and LERMAN, J.: The pituitary type of myxedema or Simmonds' disease masquerading as myxedema, Trans. Assoc. Am. Phys., 1940, lv, 32–51.

SALICYLATE TOXICITY: THE PROBABLE MECHANISM OF ITS ACTION *

By CHARLES M. CARAVATI, F.A.C.P., *Richmond, Va.*, and EDGAR F. COSGROVE, *Pittsburgh, Pa.*

FOR years it has been customary to administer alkalis in conjunction with oral salicylate therapy, based on the assumption that sodium bicarbonate protects the stomach by inhibiting the release of salicylic acid.[1] However, not until the recent work of Coburn [2] has it become customary to administer massive doses of salicylates over a protracted period. He advocates the intravenous and oral administration of sodium salicylate until a blood plasma level of over 300 gammas per c.c. is reached, and recommends that it be maintained at a high level for some weeks. In the application of this therapeutic procedure in our hands, in a comparatively small series of cases we were impressed that patients receiving salicylates intravenously experienced more nausea and vomiting than patients who received it orally. To establish clearly the mode of action of salicylate, a series of cases was analyzed and various studies performed and data assembled to determine the toxic action of salicylates particularly on the gastrointestinal tract.

1. A Comparative Clinical Review. A number of patients were given sodium salicylate by the intravenous route and blood level determinations made twice daily. A similar number were given equal doses of salicylate orally and salicylate levels determined twice daily. The level of salicylate in the peripheral blood was noted when nausea developed in each case in each group. Although it can be seen from table 1 that nausea and even vomiting

TABLE I

Occurrence of Nausea during Salicylate Therapy

	Mean Plasma Salicylate Level (gammas per c.c.)	% Patients with Nausea
Group 1 Intravenous salicylate	372	58
Group 2 Oral salicylate	366	48

were experienced in both series, a larger number of patients who received the drug by the intravenous route experienced nausea than those to whom it was administered orally. Although it was demonstrated clearly that there was marked fluctuation in the blood level during the 24 hour period following the intravenous administration, and although higher peaks were reached than were possible by the oral route, more constant and stable levels were maintained by the latter method.

* Received for publication August 27, 1945.

2. Simultaneous Administration of Sodium Bicarbonate and Sodium Salicylate. Smull [8] and her co-workers have shown that the administration of sodium bicarbonate would promptly and materially reduce the serum salicylate level and that the simultaneous administration with salicylate drugs will prevent attaining a satisfactory elevated level. In the two groups of patients studied above, Group 1, receiving salicylates intravenously, and Group 2, receiving it orally, sodium bicarbonate was administered soon after nausea appeared. In each group, there was a prompt amelioration of the nausea, and within 12 hours there was no gastrointestinal dysfunction. Another study of the blood salicylate level in these cases after 24 hours showed that there was a marked and prompt reduction of the level that had been attained prior to giving the alkali, and that this reduction was about equal in both groups, as seen in table 2.

TABLE II

Plasma Salicylates before and after Sodium Bicarbonate

	Mean Salicylic Level (Pre-Soda)	Mean Salicylic Level (24 hrs. after Soda)
Group 1 Intravenous salicylate	330	195
Group 2 Oral salicylate	295	188

3. Urinary Excretion of Salicylates. Although Smull et al.[3] emphasized that alkali should not be given simultaneously with salicylates as it prevented the attainment of a high blood level, they did not indicate the mechanism of this action. In the patients studied by us while administering sodium bicarbonate, quantitative urinary determinations for salicylic acid were performed. As can be seen from the table below (table 3), the administration of sodium bicarbonate will increase the urinary excretion of salicylate promptly, and in general, the higher the pH of urine, the greater the excretion of salicylates. Just as would be expected, there is a corresponding drop in the serum salicylate level as the urinary excretion increases. And further, by lowering the pH of the urine by the oral administration of ammonium chloride, the urinary excretion of salicylic acid is retarded and there occurs

TABLE III

Plasma and Urinary Salicyl before and after Alkali

Patients	Mean Plasma Level	Mean Plasma Level	Urine Salicyl	Urine Salicyl
	Pre-Soda	Post-Soda	Pre-Soda	Post-Soda
Case 1	320	184	444	595
Case 2	295	176	276	470
Case 3	392	264	470	523
Case 4	412	294	392	742
Case 5	304	192	260	448

a reciprocal increased concentration in the blood. In several cases after a relatively constant plasma salicylic level has been attained by the administering of a given quantity of salicylates, the administration of 3 to 8 grams of ammonium chloride orally would cause a prompt and sustained rise in the plasma level with a corresponding drop in the pH of the urine. The following case report illustrates these clinical and laboratory findings.

T. G., a white male, aged 23, was given 1.66 grams of sodium salicylate every four hours (a total of 10 grams daily) beginning three days after an attack of monocyclic rheumatic fever with fibrinous pericarditis. After three days of salicylate administration, the plasma level ranged from 260 to 280 gammas per c.c. At the same time the pH of the urine ranged from 6.3 to 6.6. At this time ammonium chloride, 4 grams daily, was given and within two days the plasma level rose to between 350 and 400 gammas and remained as long as the pH of the urine ranged from 4.7 to 5. Later, when ammonium chloride was discontinued and the urinary pH rose to 6.2, the plasma level dropped to 260 gammas per c.c.

4. Gastric Secretion of Salicylate. The favorable response from alkalis in the relief of the toxic symptoms from salicylates, administered either orally or intravenously, necessitated investigation to determine whether the effective relief was due to the prevention of local gastric reaction by the salicylates, or whether it may have been central in action. A group of cases was then studied, in which salicylates were administered intravenously until a high and fairly constant level was attained and tinnitus and nausea occurred, at which time gastric intubation was performed and the aspirated contents were analyzed quantitatively for titrable acidity and for the presence of salicylic acid in the stomach. In no case was there found any significant variation from the already determined basal acid secretion, nor was even a trace of salicylic acid found in the contents in any of the 15 consecutive cases in which the intubation was performed when the salicylic blood level was over 250 gammas per c.c. In several other patients a high level was attained by giving oral salicylate and from six to eight hours after the final oral dose was administered, gastric aspirations were performed and no evidence of salicylic acid was found in the contents removed from these stomachs. These convincing findings would seem to disprove the time-honored teaching that the nausea and vomiting experienced during salicylism are due to the presence of salicylic acid within the gastric lumen. Though salicylate permeates practically all body tissues and can be quantitatively measured in the saliva, spinal fluid, bile, synovial fluid, feces and urine, no trace of free salicylic acid has yet been found in the gastric contents of our patients receiving salicylates.

5. Gastroscopy. Twenty cases receiving salicylate therapy were gastroscoped in order to study the appearance of the stomach mucosa while toxic from salicylates.

Hurst and Lintott,[4] in 1939, reported hematemesis after the administration of aspirin and it has been quite uniformly accepted that salicylic acid and its compounds produce gastric irritation. For this reason, it has been cus-

tomary to advise against the oral consumption of aspirin in cases with peptic lesions or other gastric disturbances. These reactions are probably due to an unexplained hypersensitivity, and may occur after the ingestion of even a very small amount of the drug. William D. Paul [5] studied 228 cases before and after the oral administration of aspirin, and concluded that it did not cause irritation of the gastric mucosa in any cases studied by him. In 12 patients given intravenous salicylates, gastroscopic examinations were performed by us when the blood levels were over 300 and the patient was experiencing nausea or mild gastric unrest. Adequate visualization of the exposed gastric mucosa was accomplished in each case, and no evidence of any abnormality was seen in any case. Gastroscopic examinations were made in eight cases who had been receiving 12 grams of salicylates daily by mouth, two of whom were experiencing nausea at the time of the examination. No significant abnormalities of the gastric mucosa were observed in any of these cases except that one showed increased highlights and minimal superficial gastritis. These findings would indicate that no significant adverse effect upon the gastric mucosa results from either oral or parenteral salicylate therapy.

TABLE IV

Gastroscopic Studies of Patients Receiving Salicylates

Method of Administration	Number of Patients	Number Showing Pathology
Intravenous	12	0
Oral	8	1

SUMMARY

1. Intravenous salicylates produce nausea, vomiting and dizziness as frequently as do oral salicylates.

2. Alkalis promptly reduce the blood level of salicylates by increasing urinary salicylate excretion.

3. Blood salicyl levels are dependent on size of the dose and the pH of the urine. The lower the urinary pH, the higher the plasma level of salicylates.

4. Salicylates are not found in gastric aspirates regardless of the height of the plasma levels.

5. Gastroscopy in 20 cases has failed to reveal any significant abnormal mucosal changes occurring during salicylism.

CONCLUSION

The data presented seem to indicate that the gastrointestinal symptoms noted during salicylate therapy are due to its action on the cerebral centers and not to any local effect on the alimentary tract.

BIBLIOGRAPHY

1. Schnedorf, J. G., Bradley, W. B., and Ivy, A. C.: Effect of salicylic acid upon gastric activity, and the modifying action of calcium gluconate and sodium bicarbonate, Am. Jr. Digest. Dis., 1935, iii, 239–244.
2. Coburn, A. F.: Salicylate therapy in rheumatic fever, a rational technique, Bull. Johns Hopkins Hosp., 1943, lxxiii, 435–464.
3. Smull, Catherine, Wegria, Rene, and Leland, Jessica: The effect of sodium bicarbonate on serum salicylate level during salicylic therapy of patients with acute rheumatic fever, Jr. Am. Med. Assoc., 1944, cxxv, 1173–1175.
4. Hurst, A., and Lintott, G. A. M.: Aspirin haematemesis—clinical and gastroscopic study, Guy's Hosp. Rep., 1939, lxxxix, 173–183.
5. Paul, William D.: The effect of aspirin on gastric mucosa, Jr. Iowa Med. Soc., 1943, xxxiii, 155–158.

THE PLASMA VOLUME IN LAENNEC'S CIRRHOSIS OF THE LIVER *

By GEORGE A. PERERA, M.D., *New York, N. Y.*

IT has been previously observed that the increase in plasma volume, frequently encountered in patients with cardiac insufficiency, appears to be associated with right-sided failure.[1] The suggestion that this may be due to dilatation of the portal circulatory bed in response to elevation of the venous pressure has led to the present study. In order to determine a possible relationship between portal hypertension and the plasma volume, measurements were made in a group of patients with cirrhosis of the liver.

MATERIAL AND METHODS

Ten patients with Laennec's cirrhosis were studied on the wards of the Presbyterian Hospital. The clinical diagnosis was confirmed by histologic examination (after surgery or post mortem) in three, and a presumptive diagnosis [2] was made in the remainder by a compatible history and physical examination, laboratory tests revealing abnormal liver function, and such evidence as hepatosplenomegaly, signs of collateral circulation, non-obstructive jaundice and ascites when present. Cases that were equivocal and those with diabetes or abnormal pigmentation were excluded from this series. Although edema was present in five patients, none gave a history or showed signs or symptoms of cardiac disease. The venous pressure was measured in five cases and was within normal limits.

In the presence of significant ascites, patients were weighed after paracentesis to minimize any error in the calculation of surface area, and these weights did not differ markedly from the average weight of the patient before the onset of cirrhosis. The cephalin flocculation test [3] was positive in varying degrees in all patients, and the bromsulfalein test was carried out on six patients by the injection of 5 mg. of dye per kilo of body weight. Blood samples for hematocrit and volume measurements were obtained with the patient lying flat in bed, and after at least a 20 minute period of inactivity in that position. The plasma volume was determined with the blue dye T. 1824, the optical density being measured with the photoelectric colorimeter.[4] Multiple serum samples were obtained 10 to 20 minutes after intravenous injection of the dye, predicted values being based on the data of Gibson and Evans [5] and the observed hematocrit. The difference between observed and predicted values was expressed as a percentage deviation from normal.

* Received for publication September 18, 1945.
From the Department of Medicine, Columbia University College of Physicians and Surgeons and the Presbyterian Hospital, New York City.

TABLE I

Clinical and Laboratory Data in 10 Patients with Cirrhosis

Case	Sex	Age	Weight kilos	Height cm.	Surface Area sq.m.	Liver —cm. below costal margin in midclavic. line	Splenomegaly	Ascites	Collateral Circulation		Hgb Gm.	RBC mill. per cu.mm.	Hematocrit per cent cells	Cephalin Flocculation	Bromsulf. per cent retention in 30 mins.	Gm. per 100 c.c. serum		Predicted Plasma Volume c.c.	Plasma Volume c.c.	Deviation from Predicted Plasma Volume per cent
									Abnormal Abdominal Veins	Esophageal varices						Alb.	Glob.			
1	M	48	74	177	1.91	3	0	0	0	0	14.0	4.9	48	++	20	3.2	3.0	2985	3240	+ 8
2	M	47	68	177	1.84	3	0	0	0	0	10.5	3.5	48	++		3.3	4.1	2860	2695	− 6
3	F	54	53	155	1.50	4	0	+	0	0	10.5	4.3	39	+++		2.0	5.7	2380	2585	+ 9
4	M	52	58	162	1.65	4	+	+	+	0	11.0	3.5	47	++++		2.5	5.1	2530	3065	+21
5	M	63	60	164	1.65	6	+	0	+	+	14.0	4.4	45	+++	50	4.0	3.7	2625	2910	+11
6	M	64	70	170	1.81	0	+	+	+	0	13.1	4.9	40	++	35	2.9	2.0	3240	3825	+18
7	F	61	81	162	1.86	0	0	+	+	+	10.5	3.4	35	++	60	2.5	3.0	2730	3200	+17
8	F	52	61	160	1.63	11	+	+	+		12.2	3.8	37	+++		3.8	3.1	2555	2845	+11
9	F	36	53	155	1.50	6	+	+	+		12.5	3.0	38	+++	50	2.2	3.9	2420	3040	+25
10	M	34	64	181	1.82	0	+	+	+	+	12.5	3.7	41	++++	15	2.8	3.4	3185	3835	+20

TABLE II

Clinical and Laboratory Data in a Patient with Inferior Vena Cava Obstruction

11	M	37	84	180	2.04	6	+	+	+		13.0	4.6	42	0	5	2.5	3.5	3596	4520	+26

Results

The results are shown in table 1. It is apparent that the majority exhibited an increased plasma volume, seven of 10 patients having values greater than 10 per cent above the predicted normal.

The three patients (cases 1–3), whose plasma volume fell within 10 per cent of the predicted values, showed no splenomegaly, abnormal abdominal veins or esophageal varices by barium roentgenographic studies, although one (case 3) had moderate ascites and edema in association with a serum albumin concentration of 2 gm. per 100 c.c. In the seven patients (cases 4–10) whose plasma volumes were greater than 10 per cent above the predicted values, abnormal veins or varices or both were invariably present, and the spleen was palpable in all but one. In one case a direct measurement of portal vein pressure was made at operation, an increase to 290 mm. of water being recorded.

The rise in plasma volume was unrelated to the degree of liver enlargement. The three patients without significant change in plasma volume all showed hepatomegaly, while no liver enlargement was demonstrated in three patients with plasma volume increases varying from 17 to 20 per cent above predicted values.

From the data it is also apparent that plasma volumes could not be correlated with the intensity of cephalin-cholesterol flocculation, degree of bromsulfalein retention, or serum albumin and globulin concentrations.

Discussion

The increase in plasma volume in the majority of the cirrhotic patients studied cannot be explained by loss of dye in ascitic fluid. Examination of centrifuged ascitic fluid before and after dye injection in one patient with an elevated volume showed no change in colorimeter readings and similar conclusions have been reached by other observers.[6] Although delayed mixing was present in those with increased volumes, a constant disappearance slope following mixing gave no indication of any abnormal loss of dye from the circulation.

Some degree of anemia was present in many of this group. Gibson has reported an increase in plasma volume with some reduction in total blood volume in severe untreated pernicious anemia as well as reduction of red cell volume but with augmentation of blood hydration in the hypochromic anemias.[7] Although the observed increase in plasma volume might be in part attributable to anemia, the degree of hemoglobin and red cell reduction in the patients studied was not marked, hematocrit readings were essentially normal, and in some cases no significant anemia was present. Nor can hypoalbuminemia alone be responsible as a reduced plasma volume has been observed in such conditions as nephrosis and nutritional edema.[8]

It is a common clinical observation that patients with Laennec's cirrhosis may exhibit a decrease in urinary output, and that at times the tendency to

fluid retention or to diuresis is unrelated to changes in serum albumin concentration. The presence of an antidiuretic substance in the urine of some patients with cirrhosis has been recently reported.[9]

There are several reasons supporting the hypothesis that the observed increase in plasma volume may be related to portal hypertension and the secondary development of collateral venous circulation. In this series elevated volumes were regularly found in association with abnormal abdominal veins and esophageal varices. At operation or post mortem the number and caliber of collateral veins containing blood under increased pressure is often impressive. Measurement of abdominal vein diameters in several of these cirrhotic patients from infra-red photographs taken in the upright position, point toward a cross-sectional area much larger than that of the portal vein.

As added confirmation that venous obstruction results in a larger vascular bed, volume studies were carried out in a patient with obstruction of the inferior vena cava (table 2). A plasma volume 26 per cent above the predicted normal was recorded. This patient, a man of 37, developed leg varicosities, edema, and ascites over a period of several years after an upper thigh laceration. Examination also showed numerous large collateral veins over the abdomen and lower thorax, hepatosplenomegaly without laboratory evidence of significant parenchymal liver damage, hematuria and albuminuria, with a normal blood pressure and negative cardiac findings. Venous pressures were normal in the upper extremities, but markedly elevated ($\pm$ 200 mm. of water) in leg and femoral veins. There was no anemia.

The usual persistence of signs of portal hypertension after the development of a collateral circulation in cirrhosis is an indication that such an accessory venous bed does not completely replace that interfered with by the obstruction. Slow filling of compressed abdominal veins as well as circulation time measurements confirm the reduced velocity of blood flow in these collateral vessels. Other factors being equal, an increased sectional area would be required to carry this blood as a result of the reduced velocity. It would seem probable, therefore, that the increased plasma volume is due largely to such factors as distention of veins behind the point of obstruction and the increased sectional area required to handle the portal circulation in the face of a reduced velocity. It may be suggested that the increase in plasma volume is a reflection of the degree of development of the collateral circulation.

Lastly, it is of interest that the increase in plasma volume observed in the majority of cirrhotic patients studied is not as great as that found in right-sided cardiac insufficiency. In the former group the liver is scarred and possesses an impaired circulation, whereas in the latter the degree of liver engorgement may contribute a considerable increment to the plasma volume.

Conclusions

1. The plasma volume was determined in 10 patients with Laennec's cirrhosis of the liver, an increase of more than 10 per cent above predicted values being found in seven patients.

2. An increased plasma volume was also recorded in a patient with obstruction of the inferior vena cava.

3. It is suggested that the chief factors responsible for the elevated plasma volume are the distention behind the point of portal obstruction and the increased size of the collateral vascular bed required to handle the portal circulation.

BIBLIOGRAPHY

1. Perera, G. A.: The increased plasma volume in cardiac insufficiency: its correlation with right-sided failure, Jr. Clin. Invest., 1945, xxiv, 708–711.
2. Ratnoff, O. D., and Patek, A. J., Jr.: The natural history of Laennec's cirrhosis of the liver, Medicine, 1942, xxi, 207–268.
3. Hanger, F. M.: Serological differentiation of obstructive from hepatogenous jaundice by flocculation of cephalin-cholesterol emulsions, Jr. Clin. Invest., 1939, xviii, 261–269.
4. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical studies of the blood volume. IV. Adaptation of the method to the photoelectric colorimeter, Jr. Clin. Invest., 1938, xvii, 153–158.
5. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical studies of the blood volume. II. The relation of plasma and total blood volume to venous pressure, blood velocity rate, physical measurements, age and sex in ninety normal humans, Jr. Clin. Invest., 1937, xvi, 317–328.
6. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical studies of the blood volume. III. Changes in blood volume, venous pressure, and blood velocity rate in chronic congestive heart failure, Jr. Clin. Invest., 1937, xvi, 851–858.
7. Gibson, John G., II: Clinical studies of the blood volume. VI. Changes in blood volume in pernicious anemia in relation to the hematopoietic response to intramuscular liver extract therapy, Jr. Clin. Invest., 1939, xviii, 401–414.
8. Chang, H. C.: Plasma protein and blood volume, Proc. Soc. Exper. Biol. and Med., 1932, xxix, 829–832.
9. Ralli, E. P., Robson, J. S., Clarke, D., and Hoagland, C. L.: Factors influencing ascites in patients with cirrhosis of the liver, Jr. Clin. Invest., 1945, xxiv, 316–325.

SERIAL PROTHROMBIN ESTIMATIONS IN CARDIAC PATIENTS: DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS; USE OF DICUMAROL *

By Ernest Cotlove, M.D., and Jefferson J. Vorzimer, M.D., F.A.C.P., *New York, N. Y.*

Venous thrombosis with pulmonary embolism has long been recognized as an important and serious complication in postoperative surgical patients. The significance of thromboembolism in medical patients and particularly in those with heart disease is only beginning to gain adequate recognition. Pathological studies [1, 2] have shown pulmonary embolism to be the main or contributory cause of death in one-fourth to one-third of patients dying with coronary occlusion or congestive heart failure.

White [3] has recently summarized the significance of thromboembolism in heart disease. Pulmonary embolism may simulate heart disease, especially myocardial infarction; it may precipitate a severe anginal attack or even myocardial infarction in a patient with coronary disease. It may complicate heart disease, especially congestive failure and myocardial infarction, and lead to a fatal outcome in a patient who would otherwise be expected to recover. Not infrequently, massive pulmonary embolism with sudden death may occur.

Through a series of careful pathological investigations by Rössle, Neumann, Frykholm and Hunter, et al.[4] it has been demonstrated that the source of most pulmonary emboli is in bland thrombi which originate in the smaller veins of the leg and propagate upwards. Venous thrombosis was found to occur more frequently in patients in the older age groups, in those with heart disease and in those confined to bed.

The recognition of the relation of venous thrombosis and pulmonary embolism to bed rest has stimulated the recent discussions regarding the dangers of bed rest.[5, 6] There has been little investigation of changes in blood constituents in cardiac patients which might influence the occurrence of thrombosis. To contribute information regarding this aspect of the problem, we have undertaken a careful study of one element of the clotting process, the prothrombin activity of the blood, in a group of patients with heart disease, including acute myocardial infarction and congestive failure. This type of data should be of especial interest since the introduction of the newer modes of anticoagulant therapy, heparin and dicumarol † has opened new possibilities for prophylaxis and treatment.

* Received for publication February 9, 1945.

From the Medical, Surgical, Urological, Gynecological and Obstetrical Services of Beth Israel Hospital, New York City.

† "Dicumarol" is the registered collective trade-mark adopted by the Wisconsin Alumni Research Foundation for the synthetic preparation 3, 3′-methylenebis (4-hydroxycoumarin).

Methods and Material

A total of 76 individuals was studied. Thirty-two patients had evident cardiac disease, and in these, from two to 27 prothrombin determinations were done, with the exception of four cases in which only one determination was available. Nine non-cardiac patients with thrombo-embolism or thrombophlebitis were also followed by means of serial prothrombin times.

The control group of cases included healthy hospital workers and patients with various diseases whose nutritional status and physical condition were good. There were 35 individuals, 15 of whom were in the younger age group (between 20 and 39 years), and 20 of whom were in the older age group (between 40 and 81 years). The age distribution of the latter group was similar to that of the cardiac patients studied. In the control group, one determination was done in each of 15 cases, and from two to eight determinations in each of the remaining 20.

In the patients studied, serial prothrombin estimations were made from one to six times a week, and most cases were followed for two weeks or more, one case being studied for over three months. None of the patients received salicylates during the period of study, and vitamin K preparations and dicumarol were not given except in a few cases specifically studied. All of the patients in this series were under our close observation, and we have done or personally supervised all of the prothrombin determinations.

The method of prothrombin assay used in this study is based on the single-stage quantitative estimation described by Quick, Stanley-Brown and Bancroft [7] with the modifications introduced by Link and co-workers [8] and Shapiro.[9] Thromboplastin was prepared from rabbit lung by the vacuum desiccation method. The technic and apparatus involved in the determination have recently been clearly described by Shapiro.[10]

The method used follows in detail. To 0.5 c.c. of a 0.1 molar sodium oxalate solution are added 4.5 c.c. of blood obtained by venepuncture. The blood is centrifuged at 1700 r.p.m. for four minutes, and the plasma removed. Diluted plasma (12.5 per cent) is obtained by adding 0.1 c.c. of plasma to 0.7 c.c. of 0.85 per cent sodium chloride solution. The thromboplastin solution is prepared by adding 5 c.c. of saline to 100 mg. of the dried powdered rabbit lung, and the mixture stirred and heated at 56° C. in a water bath for 10 minutes, for extraction and in order to destroy prothrombin activity. The suspension is then cooled and 5 c.c. of a 0.025 molar solution of calcium chloride added, and the mixture centrifuged at 1700 r.p.m. for four minutes. The supernatant solution is removed for use. Whole and diluted plasma samples are placed in a rack in a constant temperature water bath (37.5° C.). Into 10 by 75 mm. test tubes, 0.2 c.c. of the thromboplastin-calcium chloride solution is transferred, and these tubes are also placed in the rack. The clotting times are determined after six minutes, when the contents of the tubes have reached bath temperature. Using a 0.1 c.c. micro blood sugar pipette, 0.1 c.c. of whole plasma is rapidly blown into a tube

containing the thromboplastin-calcium chloride solution, and the stop-watch, operated by a pedal, is started. A platinum wire stirrer with a loop at the end is moved slowly back and forth across the test tube until the end-point is reached, when the watch is stopped. The end-point for whole plasma is taken as the instant when the clot begins to move with the loop. The same procedure is repeated, using diluted plasma,* the end-point here being the moment when the whole clot can be lifted as a unit, which occurs from one to several seconds after the clot first begins to form. Duplicate determinations were done in most cases.

Results

Normal Values of Prothrombin Time. 1. Control Series. These data include the 35 individuals previously described, and are given in table 1. The averages and standard deviations shown are calculated from the average of the serial determinations for each individual. The averages, divided according to age and sex, are also noted.

Table 1

Control Series

	Number of Cases	Whole Plasma Prothrombin Time (sec.)		12.5% Diluted Plasma Prothrombin Time (sec.)	
		Average	Standard Deviation	Average	Standard Deviation
Total group	35	17.8	±2.0	45.2	±5.0
Older age group (40–81 yrs.)	20	18.5	±2.0	45.2	±5.0
Younger age group (20–39 yrs.)	15	16.9	1.4	45.3	4.5
Older age group					
Males	12	18.7		46.1	
Females	8	18.0		44.0	
Younger age group					
Males	8	17.5		45.9	
Females	7	16.0		43.1	
Total (males)	20	18.3		46.0	
Total (females)	15	17.1		43.6	

2. Influence of vitamin K on prothrombin time of normals. Five normal individuals with diluted plasma prothrombin times well above the normal limits previously described for this method † were given large doses of preparations with high vitamin K activity, in order to observe whether the time could be shortened. None of these individuals had any evidence of liver disease. The results are noted in table 2.

* The term "diluted plasma," unless further qualified, refers to the dilution of 1 : 8 or 12.5 per cent.

† The normal standards obtained by Shapiro [10] with rabbit lung thromboplastin and employing an identical method are as follows: Whole plasma, 15.5 seconds with a standard deviation of ± 1.5 seconds; diluted plasma (12.5 per cent), 39.5 seconds, standard deviation ± 2.5 seconds.

TABLE II

Effect of Vitamin K on Prothrombin Time in Normal Individuals

Case No.	Average Prothrombin Time before Medication (seconds)		Menadione Bisulfite Total Dose	Duration of Medication	Average Prothrombin Time after Medication (seconds)	
	Whole Plasma	Diluted Plasma	(Mg.)	(Days)	Whole Plasma	Diluted Plasma
1	16	47	50	11	17	48
2	16	48	12	3	18	52
3	16	56	24	8	17	58
4	18	44	50	5	17	41
5	17	48	50	4	17	46

Individual Variation of Prothrombin Time. The average and standard deviation, and the range of the prothrombin time in serial determinations for each of seven individuals are shown in table 3. These include normal individuals and those with heart disease, but none received medication.

TABLE III

Individual Variation in Prothrombin Time *

Case No.	Number of Determinations	Prothrombin Time (seconds)			
		Whole Plasma		Diluted (12.5%) Plasma	
		Average and Standard Deviation	Range	Average and Standard Deviation	Range
1	13	17.3 ± 1.6	15–21	48.2 ± 2.5	44–54
2	15	17.5 ± 1.4	15–20	38.7 ± 2.2	36–43
3	14	18.9 ± 2.0	16–22	43.4 ± 2.4	35–50
4	14	18.5 ± 2.5	15–23	38.5 ± 2.6	31–45
5	8	18.3 ± 1.3	16–21	44.4 ± 2.6	40–48
6	8	16.3 ± 1.3	14–17	57.3 ± 2.7	53–62
7	8	17.3 ± 1.1	16–19	42.6 ± 3.3	40–48

* This series includes normal individuals and patients with heart disease.

Effect of Digitalis on Prothrombin Time. The results are given in table 4. Digitalization was effected rapidly (within 24 hours) or over a period of days, and maintenance dosage continued. The total period of digitalis medication is noted.

In addition, there were 11 cases who had been taking maintenance doses of digitalis for periods of two weeks to many months before admission. The average prothrombin time in this group was 18.8 seconds (whole plasma) and 47.9 seconds (diluted plasma).

The average prothrombin time of all 18 cases who received digitalis was 19.0 seconds (whole plasma) and 47.5 seconds (diluted plasma).

One patient received 3.6 gm. digitalis leaf in four days and developed toxic signs but there was no change in prothrombin time.

Effect of Bed Rest and Ambulation on Prothrombin Time. Fourteen patients were studied who were confined to bed for varying periods of time,

TABLE IV

Effect of Digitalis on Prothrombin Time in Cardiac Patients

Case No.	Prothrombin Time before Digitalis (seconds)		Prothrombin Time after Digitalization (seconds)		Duration of Digitalis Medication (days)
	Whole Plasma	Diluted Plasma	Whole Plasma	Diluted Plasma	
1*	18	47	18	47	12
2	18	41	19	43	2
3	19	36	18	36	3
4	16	44	17	42	1
5	20	44	19	46	2
6	20	59	23	60	11
7	21	54	20	52	8

* This patient developed toxic manifestations after receiving 3.6 gm. of digitalis leaf in four days.

from seven to 52 days. In 10 of these, prothrombin determinations were available at the onset of bed rest or shortly thereafter, during the course of bed rest and at its termination, and also after several days or more of ambulation. The data are given in table 5.

TABLE V

Effect of Bed Rest and Ambulation on Prothrombin Time in Cardiac Patients

Case No.	Duration of Bed Rest (days)	At Onset of Bed Rest*		Average Prothrombin Time (seconds)			
				At End of Bed Rest		After Ambulation†	
		Whole Plasma	Diluted Plasma	Whole Plasma	Diluted Plasma	Whole Plasma	Diluted Plasma
1	25	18	39	17	37	17	40
2	31	21	44	19	44	17	41
3	30	19	41	18	38	19	41
4	23	19	43	18	47	17	45
5	12	16	36	17	38	18	33
6	52	18	39	18	47	16	47
7	7	20	43	19	45	18	44
8	14	21	47	21	52	15	45
9	14	18	42	19	46		
10	26			21	68	20	65
11	15			17	47	18	48
12	10	20	59	23	58	23	60
13	12	23	60	20	52		
14	7	18	47	17	46	18	50

* First determinations were made within one to five days after onset of bed rest except in one case.

† Determinations were made after three days or more of ambulation.

Prothrombin Time in Congestive Heart Failure. A total of 20 patients is included, in which serial prothrombin determinations were done in the presence of failure. The average prothrombin time for each case, and the averages for the groups are noted and classified according to the degree of failure (table 6).

TABLE VI

Prothrombin Time in Congestive Heart Failure

Degree of Failure*	Mild*		Moderate*		Advanced*	
Number of cases	7		11		2	
	Whole Plasma (seconds)	Diluted Plasma (seconds)	Whole Plasma (seconds)	Diluted Plasma (seconds)	Whole Plasma (seconds)	Diluted Plasma (seconds)
Average prothrombin time of all cases in each group:	18	43	19	50	18	47

* Degree of failure represents the extent at the time of prothrombin estimation.
Mild degree: slight venous distention, liver at or just below costal margin, 0 to 1+ edema.
Moderate degree: moderate venous distention, liver 2 to 4 cm. below costal margin and tender, 1 to 2 + pitting edema.
Advanced degree: marked venous distention, hydrothorax, liver below umbilicus and tender, 3 to 4+ pitting edema.

Prothrombin Time in Recovery from Congestive Failure. Nine individual cases were followed with serial prothrombin times during the course of recovery from congestive failure. Only patients with moderate or advanced degrees of decompensation who showed marked improvement during observation were included. The findings are presented in table 7.

TABLE VII

Prothrombin Time in Recovery from Congestive Failure *

Average Prothrombin Time (seconds)

Case No.	During Congestive Failure		After Recovery	
	Whole Plasma	Diluted Plasma	Whole Plasma	Diluted Plasma
1	21	44	19	45
2	19	41	18	39
3	16	36	17	36
4	20	44	19	45
5	21	47	15	45
6	24	58	16	47
7	18	42	20	45
8	20	59	23	60
9	21	55	20	52

* All patients included in this group had moderate or advanced degrees of congestive failure which improved markedly or cleared completely during observation. All received digitalis.

Prothrombin Time in Coronary Occlusion. Five patients with acute coronary occlusion were studied. The initial estimation was obtained five days after onset in two cases and between 11 and 24 days after onset in three. The average time of the five cases was 19.8 seconds (whole plasma) and 43.4 seconds (diluted plasma). The shortest diluted plasma time was 39 seconds (in two cases) and the longest time was 50 seconds.

Prothrombin Time in Angina Pectoris. Five patients were studied during the course of repeated attacks of angina pectoris. The overall average

of the mean times for each was 18.2 seconds (whole plasma) and 45.9 seconds (diluted plasma). On one occasion, in one of the patients, a severe anginal attack was coincident with an abnormal acceleration of the diluted plasma prothrombin time to 34 seconds, with no change in whole plasma time.

Prothrombin Time in Mural Thrombosis with Embolism. Two patients were observed in whom myocardial infarction was followed in several weeks by arterial embolism, indicating the presence of left ventricular mural embolism. Prothrombin study was begun a few days after embolism. The average times in the first case were 18 seconds (whole plasma) and 41 seconds (diluted plasma). In the second case the times were 23 seconds and 39 seconds respectively. Three patients were observed who had rheumatic heart disease, auricular fibrillation and multiple embolism (pulmonary and systemic) indicating auricular thrombi. One case showed an average prothrombin time of 21 seconds (whole plasma) and 60 seconds (diluted plasma). The other two patients were treated with dicumarol before adequate base values were obtained, but the marked reaction to dicumarol exhibited in both indicated that there was no increase in prothrombin activity.

Prothrombin Time in Thrombo-embolism and Thrombophlebitis. A total of eight cardiac patients with pulmonary embolism and infarction was studied by means of serial prothrombin estimations. Four of the patients showed no deviation from the normal prothrombin time; three patients showed a slight, relative shortening of diluted plasma time in comparison with the usual (or normal) value for each individual; only one patient showed a definite abnormal shortening of the diluted plasma prothrombin time (34 seconds) and this was three days after operation.

There were five non-cardiac patients studied who showed thromboembolism. These included three postoperative patients, one pregnant patient at term, and one with thrombophlebitis and pulmonary embolism. Four of these cases showed an abnormal acceleration of diluted plasma prothrombin times taken one to three days after the occurrence of embolism, the times being from 29 to 34 seconds (diluted plasma). In the fifth patient the time was 42 seconds (diluted plasma). The whole plasma times were normal.

Four patients were observed who had thrombophlebitis of the leg veins without embolism; one of these was a cardiac patient. In only one of the group (a non-cardiac patient) was an abnormal acceleration of the diluted plasma time observed (33 seconds); in the other cases, the times were within normal limits.

In the course of the entire study, apart from the cases cited above, an abnormal acceleration of diluted plasma prothrombin time was encountered on only three occasions: in one case, without evident cause; in a second instance occurring two weeks later in the same patient there was a simultaneous occurrence of a severe attack of chest pain which may have represented a pulmonary embolus; in the third case the diagnosis was pneumonia,

but pulmonary infarction could not be excluded. The diluted plasma prothrombin times in these three instances were between 31 and 33 seconds.

Administration of Dicumarol to Cardiac Patients. Six cardiac patients were given dicumarol therapeutically. All of these patients had evidence of embolism. The dosages and responses are briefly summarized.

1. A patient with arteriosclerotic heart disease and pulmonary infarction received 1.0 gm. of dicumarol in 10 days, with subsequent rise of whole plasma prothrombin time to 65 seconds.

2. A patient with rheumatic heart disease and auricular thrombosis with embolism received 1.0 gm. of dicumarol in 16 days, with rise of whole plasma prothrombin time to 80 seconds.

3. A patient with rheumatic heart disease, auricular thrombosis with multiple embolism who was critically ill, showed a rise of whole plasma prothrombin time to 48 seconds three days after a single dose of 300 mg. of dicumarol, with slow return to normal values over the period of a week.

4. A patient with arteriosclerotic heart disease developed pulmonary embolism three days postoperatively showed an abnormally accelerated diluted plasma prothrombin time (34 seconds). He was given 500 mg. of dicumarol in two days and three days later showed a rise in whole plasma prothrombin time to 170 seconds, with bleeding from the operative wound. He was given a 500 c.c. fresh blood transfusion and 100 mg. of an active vitamin K preparation (menadione bisulfite) in the next three days. Following the transfusion, there was an immediate cessation of bleeding, and the prothrombin time fell to normal levels and was maintained. The subsequent administration of 100 mg. of dicumarol produced no change in prothrombin time. The patient was critically ill in the first week following pulmonary embolism, but he subsequently made a fairly rapid recovery.

5. A patient with acute myocardial infarction and suggestive signs of pulmonary embolism was given 600 mg. of dicumarol in seven days, with rise of whole plasma prothrombin time to 75 seconds.

6. A patient with rheumatic heart disease, thrombophlebitis and pulmonary infarction received 350 mg. of dicumarol in five days, with rise of whole plasma prothrombin time to 40 seconds.

Discussion

Validity of Method of Prothrombin Estimation. The method of prothrombin estimation used in this study is based on the single-stage quantitative estimation first described by Quick, Stanley-Brown and Bancroft.[7] Link and his associates[8] and Shapiro[10] have introduced certain modifications which have increased the value and accuracy of the method. Estimation of prothrombin time with diluted plasma enables the detection of small changes in prothrombin activity which would not be evident with whole plasma. The explanation for this resides in the relation between the concentration of prothrombin to the clotting time. In the higher concentration range of prothrombin, wide variations in prothrombin concentration cause

relatively slight changes in the clotting time, whereas in the concentration range below 25 per cent even small variations in prothrombin concentration result in marked changes in the clotting time (Quick [11]). In addition, the naturally occurring anticoagulants present in blood in varying activity are rendered largely ineffective by plasma dilution (Link [8]). The dilution of 1:8 (12.5 per cent) has been found most useful in studies on human patients (Shapiro,[9, 10] Brambel and Loker [12]).

The Normal Values of Prothrombin Time. It is necessary to ascertain the normal values for the prothrombin time and the normal range of variability for the individual and group before the significance of observed changes under certain experimental conditions can be properly interpreted. Reports from various laboratories show that the normal value may be different for each laboratory, and the "normal" for the whole plasma prothrombin time has been reported in the range between 10 and 25 seconds. In this study, rabbit lung thromboplastin prepared by the vacuum desiccation method was used because of its high degree of consistency. The technic outlined by Shapiro [10] was followed in detail. Our control values show some difference from his results. The normal standards reported for the method by Shapiro are: 15.5 seconds, standard deviation 1.5 seconds for whole plasma; 39.5 seconds, deviation 2.5 seconds (12.5 per cent) diluted plasma. Our control figures are: 17.8 seconds, deviation 2.0 seconds (whole plasma); 45.2 seconds, deviation 5.0 seconds (diluted plasma). The lack of effect of vitamin K on the clotting times of some of the control cases indicates that the higher values obtained by us were not due to dietary deficiency and were probably normal values. The greater standard deviation which we found necessitates more caution in the interpretation of slight deviations from the normal. It should be noted that the individual variability in prothrombin times was found to be considerably less than the group variability. Slight changes in the serial prothrombin times of any one individual, especially if consistent, may have significance. No significant age or sex difference was found.

Effect of Digitalis on Prothrombin Activity. There have been few reports on the effect of digitalis on the coagulation mechanism, although it would be important to determine whether the widespread use of this drug influences the formation of thrombi. Werch,[13] Macht [14] and de Takats, et al.[15] reported work on animals indicating that digitalis preparations increase the coagulability of the blood. Massie and co-workers [16] reported work which indicated that digitalis given in therapeutic doses to human patients results in a shortening of the whole blood coagulation time but has no effect on prothrombin time as measured by the Smith bedside test.

Our results do not demonstrate any effect of digitalis on the prothrombin time of whole or diluated plasma, whether the digitalis is given for short, or long periods, whether digitalization is effected rapidly or slowly, and even if a toxic dose is given.

There is no clear evidence up to the present time that therapeutic doses

of digitalis in human patients increase the coagulability of the blood or the tendency to thrombosis, and digitalis should not be withheld because of such fears, where it is indicated. The statistics of Williams and Rainey [2] indicate that the control of congestive failure reduces the incidence of leg vein thrombosis.

Effect of Bed Rest and Ambulation on Prothrombin Activity. There is much evidence, previously noted,[4] that prolonged bed rest greatly increases the incidence of venous thrombosis and pulmonary embolism. The recent discussions of the dangers of bed rest have emphasized this problem.[5, 6] The reasons for this increased incidence are not fully understood, although the mechanical factors involved seem to be fairly evident. According to our data, there is no evidence that bed rest or ambulation, per se, has any effect on the prothrombin activity of the blood. When thrombophlebitis or thromboembolism occurs, however, the prothrombin time may change in some cases, as will be discussed more fully below. It should be emphasized that thrombosis and embolism not infrequently occur in patients who have not been confined to bed. This has been noted by other authors [17, 18] and we have encountered it as well.

Prothrombin Activity in Congestive Heart Failure. The liver has been shown to be the main site of prothrombin production.[19] Since the plasma prothrombin level is affected by liver function, it might be expected that the hepatic congestion occurring in cardiac decompensation would result in an appreciable reduction in prothrombin activity. Previous work [20] has demonstrated some impairment of liver function in right heart failure. On the other hand, the high incidence of thrombo-embolism in congestive failure might have some relation to an increase in prothrombin activity.

The prothrombin activity in congestive heart failure, as measured by the whole and diluted plasma prothrombin times in our group of patients, showed no significant change in either direction. The average prothrombin times of patients with various degrees of failure showed little difference, and the serial prothrombin times of individuals recovering from failure showed no significant change. The average prothrombin time of all of the patients with cardiac decompensation was not different from the normal values of the control series.

Prothrombin Activity in Thrombo-Embolism. Shapiro and his associates, in a series of papers,[9, 13, 21, 22] have presented evidence of an increase in prothrombin activity occurring in acute thrombophlebitis and thromboembolism. In these cases, they found an acceleration of the diluted plasma prothrombin time beyond the normal limits, while the whole plasma time was normal or prolonged. Shapiro, Sherwin and Gordimer [21] found that increased prothrombin activity, in the form of an accelerated diluted plasma prothrombin time, was present in the majority of postoperative patients, occurring in the second week following operation. In a few cases, a marked increase in prothrombin activity was noted to precede the occurrence of pulmonary embolism by several days. Brambel and Loker obtained similar

results in postoperative patients and patients with phlebitis. The only other condition in which an abnormally short diluted plasma prothrombin time has been consistently reported is parturition.[23] At the present time, the evidence indicates that any acceleration of diluted plasma prothrombin time beyond the normal limits does not occur under normal circumstances.

The data previously reported have been based on studies of surgical and obstetrical patients almost entirely. In our investigation of eight cardiac patients with thrombo-embolism, followed by means of serial prothrombin determinations, the characteristic abnormal acceleration of the diluted plasma prothrombin time was seen in only one, and in this patient it was also three days after operation. Four patients showed no change, but three gave indication of a relative acceleration of the diluted plasma time; however, this could be established only by prior or subsequent determinations to ascertain the normal level for the particular patient. In contrast, four of five non-cardiac patients who developed venous thrombosis and pulmonary embolism showed the characteristic acceleration of the diluted plasma prothrombin time, in confirmation of the previous work cited.

The difference in the findings between the cardiac and non-cardiac groups of patients is of interest. The significance of an abnormally shortened diluted plasma prothrombin time is not definitely known. It may represent an increased prothrombin concentration or activity (hyperprothrombinemia) or it may be related to factors, other than prothrombin, which are affected by dilution, such as anticoagulants, protein fractions, or other unknown quantities. Shapiro [10] feels that it represents a true hyperprothrombinemia, which is not reflected in the whole plasma prothrombin time because of the presence of interfering anticoagulant substances. The absence of response (increased prothrombin in the presence of thrombosis) in the cardiac patients we have studied, may be related to an inability to produce excess prothrombin or it may reflect other changes in the plasma protein fractions of the cardiac cases. Shapiro [24] has reported an abnormal acceleration of diluted plasma prothrombin time in a case of multiple myeloma with a markedly elevated serum globulin, indicating that a change in the protein fractions of the blood may affect the prothrombin time as measured independently of the actual prothrombin concentration. It is true that our cardiac patients had complications such as congestive failure, myocardial infarction or bronchopneumonia, and were in general in poorer physical condition than the postoperative and postpartum group who were otherwise healthy individuals.

The significance of an accelerated diluted plasma prothrombin time in relation to intravascular thrombosis is difficult to determine. This finding may precede the occurrence of recognizable venous thrombosis or pulmonary embolism by several days, but it frequently is coincident with thrombo-embolism or appears a few days subsequently. If the increased prothrombin activity is presumed to be a causal factor in thrombosis, the latter observation is difficult to explain. Furthermore, it is not apparent in what way an ac-

celeration of prothrombin conversion by a few seconds could influence the occurrence of intravascular thrombosis. Warner et al.[25] have demonstrated a more rapid conversion of prothrombin in dogs and other animals though thrombosis is not more frequent. Shapiro [10] has noted that in cases of arterial embolism or thrombosis there is no shortening of the diluted plasma prothrombin time. No changes in prothrombin time were observed in our cases of coronary thrombosis, peripheral arterial embolism and thrombosis, or mural thrombosis of the cardiac chambers. The acceleration of the diluted plasma prothrombin time seen in cases of venous thrombosis may be an effect rather than a cause of the thrombosis, in that there may be an absorption of circulating anticoagulants at the site of thrombus formation. The antithrombin activity of the blood has been shown to decrease markedly during the process of clotting.[26] Diminution of anticoagulant activity would be reflected in an acceleration of prothrombin time more readily in the diluted plasma, where any remaining anticoagulant activity would be destroyed in the process of dilution. The absence of such an acceleration of prothrombin time in arterial thrombosis might then be due to the fact that venous thrombosis is usually much more extensive.

Relation of Pulmonary Embolism to Angina Pectoris and Myocardial Infarction. There have been a number of reports of the effects of pulmonary embolism on the heart. Friedberg and Horn [27] in a postmortem study of 37 cases of myocardial infarction without coronary artery occlusion, found that the most frequent cause was pulmonary embolism. Horn, Dack and Friedberg [28] and Currens and Barnes [29] reported cases with anatomic changes in the myocardium following pulmonary embolism in the presence of well-marked coronary sclerosis. Pulmonary embolism probably produces these effects by causing shock and asphyxia, which result in myocardial changes and even acute infarction in the presence of coronary sclerosis and insufficiency. Schönbrunner [29] suggested that a reflex vagal response in pulmonary embolism produced coronary spasm and cited two cases in which angina pectoris occurred after embolism and was relieved by nitrites.

In our series, one patient had two attacks of myocardial infarction, probably preceded in the first, and clearly preceded in the second, by pulmonary embolism with pulmonary infarction. The last pulmonary infarct was preceded by evidence of increased prothrombin activity and by several repeated anginal attacks which were unusually severe, which may have been precipitated by small pulmonary emboli. Another patient showed an abnormally short diluted plasma prothrombin time coincidental with a severe attack of chest pain similar to angina pectoris. Here, again, a small pulmonary embolus may have occurred.

Response to Dicumarol in Cardiac Patients. The effect of dicumarol on the prothrombin time has been set forth in a series of papers [30] which have dealt mainly with surgical patients. The average dose recommended is 300 mg. of dicumarol for the initial dose and 200 mg. the next day, with subsequent dosage dependent on the prothrombin time, the therapeutic level being

about 35 seconds (whole plasma). Elevation to 50 seconds (whole plasma) or above was found to be dangerous, with the occurrence of hemorrhage a likely possibility. Dicumarol was used in relatively few patients in this study, but the difference of its effect in these cardiac patients was so marked that the results are being reported.

Our results indicate that a dose of 500 mg. of dicumarol even when spread over a period of five to seven days caused excessive and dangerous elevations in prothrombin time in the cardiac patients. It is striking that elevations up to 80 seconds (whole plasma) did not result in bleeding. Only one patient developed hemorrhage, from an operative wound, after the administration of 500 mg. of dicumarol in two days, resulting in a very severe depletion of prothrombin. This patient responded quickly to a fresh blood transfusion and large doses of vitamin K.

On the basis of these results, it is recommended that the dosage schedule of dicumarol be reduced in treating cardiac patients. An initial dose of 200 mg. is usually safe, and the prothrombin level should be determined two days later and daily thereafter. Dicumarol may then be given, 100 mg. each day if the prothrombin time is less than 35 seconds (whole plasma) and withheld if the time is in excess of this figure. If markedly elevated prothrombin times occur despite precautions, large doses of vitamin K preparations should be given intravenously (30 mg. three to four times a day) until the time is restored to normal levels. Cromer and Barker [31] have reported on the value of massive doses of vitamin K. Where actual hemorrhage occurs, an immediate fresh blood transfusion is also indicated.

Indications for Dicumarol Therapy. 1. Coronary Thrombosis. Although Solandt and Best [32] and Dale and Jaques [33] have shown that the anticoagulants, heparin and dicumarol, can prevent intravascular thrombosis and specifically coronary thrombosis in experimental animals, the known pathological basis of coronary thrombosis in man and the relative infrequency of premonitory signs preclude any important use of these drugs in the prophylaxis of thrombosis of the coronary arteries.

2. Mural Thrombosis in Myocardial Infarction. The frequent occurrence of thrombosis overlying a myocardial infarct and the subsequent occurrence of severe and even fatal embolic episodes have been reported by a number of authors (reviewed by Blumer [34]). Blumer reports the overall incidence of mural thrombosis in myocardial infarction as 50 per cent. Solandt, Nassim and Best [35] have demonstrated experimentally that heparinization can prevent the development of mural thrombosis over an area of injured cardiac muscle. Furthermore, Mallory, White and Salcedo-Salgar [36] showed that mural thrombi do not form until the fifth day or later after infarction, and that organization of the thrombus is usually complete by the sixteenth day, being followed by the formation of a new endothelial lining. Moreover, they presented evidence that mural thrombosis is probably due to local dilatation at the site of the injured muscle and that the endothelium

almost always remains intact. This would indicate that a large infarct would be more likely to cause mural thrombosis.

In view of these considerations, it would seem valuable to administer dicumarol to patients developing myocardial infarction of a severe degree, such as would be most likely to develop large, friable mural thrombi. It is suggested that the drug be started as soon as possible after onset and continued for three weeks. The drug should be used only where facilities for doing accurate prothrombin times daily are available. The dosage schedule has been discussed. The interval of at least five days after myocardial infarction before mural thrombi begin to form allows adequate time for prothrombin depletion. The dicumarol therapy would have the added advantage of helping to prevent venous thrombosis during the initial period of required bed rest. This therapy is probably not as important in the case of the mild type of myocardial infarction, though occasionally there occurs peripheral embolism from mural thrombi following a "silent" coronary. We have begun this mode of therapy in a few cases, but a proper evaluation would require the compilation of results of treatment of a large number of cases.

3. Auricular Thrombi with Multiple Embolism. Embolism from auricular thrombi is a highly unpredictable occurrence and effects of therapy are difficult to evaluate. We have treated two cases without spectacular results. In a case with repeated, frequent embolism, dicumarol may be tried, since no other form of rational therapy is available, and it should then be given over a long period of time.

4. Thrombophlebitis, Venous Thrombosis and Pulmonary Embolism. There have been many reports on the value of dicumarol in the prevention and treatment of thrombophlebitis, bland thrombosis and embolism [30, 22, 37] and the evidence indicates that dicumarol can reduce the incidence of postoperative thrombo-embolism, prevent further embolism after it has occurred and lead to more rapid resolution of phlebothrombosis and thrombophlebitis. Our brief experience in the use of dicumarol in cardiac patients has been therapeutically satisfactory and we have not noted further embolism where the prothrombin time was adequately elevated. Dicumarol is indicated where there is clinical evidence of thrombosis or phlebitis, especially if embolism has occurred, and should be maintained for two to three weeks, with smaller doses for a longer time if possible. The patient may be allowed out of bed when the temperature is normal, provided that the prothrombin time is adequately elevated.

The question of the relative values of anticoagulant therapy and vein ligation in thrombo-embolism is undecided. Anticoagulant therapy prevents further thrombosis and probably hastens the healing of the formed thrombus; it also acts throughout the body. Vein ligation excludes the thrombus from the circulatory system, but it does not prevent thrombosis elsewhere and it is difficult to use where local signs are not present. Homans [38] has

presented an excellent discussion of vein ligation from the surgeon's standpoint. In the absence of conclusive evidence in either direction, it is suggested that dicumarol be used in the presence of thrombo-embolism, and that vein division be reserved for the infrequent cases which show recurrent embolism following institution of adequate therapy.

Summary and Conclusions

1. The method of prothrombin estimation used in this study was found to be reliable and accurate. The normal values of the prothrombin time were found to be 17.8 seconds, standard deviation ± 2.0 seconds (whole plasma) and 45.2 seconds, standard deviation ± 5.0 seconds (12.5 per cent diluted plasma). The individual variation of diluted plasma prothrombin times was about half as great as the group variation. The normal values were not changed by administration of large doses of vitamin K.

2. No effect on the whole or diluted plasma prothrombin time was observed in a group of 18 cardiac patients who received digitalis for varying periods of time. A review of the literature revealed no definite evidence that digitalis administered to patients in therapeutic doses has the effect of promoting thrombosis or embolism. Digitalis should be used in heart failure where indicated, since the control of failure is a factor in the avoidance of thrombo-embolism.

3. Bed rest for periods up to seven weeks did not produce any change in prothrombin activity, except in a few cases in which a change was associated with the occurrence of thrombo-embolism. Ambulation did not affect prothrombin activity.

4. The presence of congestive heart failure did not influence prothrombin activity, nor was any change observed following recovery from failure.

5. In the cases of coronary occlusion, as well as those with repeated attacks of angina pectoris, there was no characteristic alteration in prothrombin activity. One case developed myocardial infarction following pulmonary infarction on two occasions; during one of these there was evidence of increased prothrombin activity. Two other cases had attacks of angina pectoris probably precipitated by small pulmonary emboli, and here there was indication of increased prothrombin activity at the time of the attacks.

6. In five patients who had mural thrombosis of the cardiac chambers with embolism, no specific change in prothrombin activity was noted.

7. Eight cardiac patients developed thrombophlebitis or thrombo-embolism. In four of these there was no alteration in prothrombin time; in one case, there was an abnormal acceleration of the diluted plasma prothrombin time; and the remaining four showed a slight relative shortening of the diluted plasma prothrombin time when compared with the patient's usual level, though the times remained within the normal range. This is in contrast to the findings observed in postoperative and postpartum patients with thrombo-embolism, in which most of the patients presented an abnormally accelerated diluted plasma prothrombin time.

8. There is little known of the relation of the prothrombin activity of the blood to the occurrence of intravascular thrombosis. There is no evidence that an increase in prothrombin activity leads to thrombosis, though a marked decrease in prothrombin, such as that produced by dicumarol, can completely prevent thrombosis. The abnormal acceleration of the diluted plasma prothrombin time which has been observed in cases of thrombo-embolism may be entirely secondary to the thrombosis. There is some indication that the accelerated time which has been interpreted as evidence of increased prothrombin concentration or activity, may be related to other factors, such as changes in the protein fractions of the blood.

9. Cardiac patients appear to be more sensitive to dicumarol than others. Cardiac patients with thrombo-embolism who were given an "averaged" dose of 500 mg. of dicumarol over a period of two or more days developed excessive and dangerous elevations of the prothrombin time. The administration of dicumarol to cardiac patients or any patients in a debilitated state must be done with caution. A tentative dosage schedule for cardiac patients is suggested.

10. The therapeutic indications for dicumarol have not been established. Thrombo-embolism in cardiac patients is such an important cause of morbidity and mortality that every measure of control should be used. Dicumarol appears to be indicated in the following groups of cardiac patients: those presenting evidence of phlebothrombosis, thrombophlebitis or venous thrombo-embolism; those confined to bed in whom successive prothrombin times reveal an acceleration of the diluted plasma time even if no definite signs of thrombosis are present. The results are questionable in patients with auricular thrombosis and multiple embolism. Dicumarol is probably of no value in preventing or minimizing coronary thrombosis, but it is suggested that it be used during the first three weeks following severe myocardial infarction, in an effort to prevent mural thrombosis and venous thrombosis. Dicumarol should never be used unless there are facilities for accurate daily estimation of prothrombin time.

We gratefully acknowledge our indebtedness to Dr. Shepard Shapiro for his active assistance and encouragement throughout this study.

Miss Leah R. Blickman gave valuable technical assistance.

Dicumarol was supplied by Lederle Laboratories through the courtesy of Dr. L. M. Lockhart.

BIBLIOGRAPHY

1. Eppinger, E. C., and Kennedy, J. A.: The cause of death in coronary thrombosis, with special reference to pulmonary embolism, Am. Jr. Med. Sci., 1938, cxcv, 104–106.
2. Williams, R. H., and Rainey, J.: Cause of death in patients with congestive heart failure, Am. Heart Jr., 1938, xv, 385–394.
3. White, P. D.: Heart disease, 3rd Edition, 1944, Macmillan Co., New York, N. Y.
4. Hunter, W. C., Sneeden, V. D., Robertson, T. D., and Snyder, G. A. C.: Thrombosis of the deep veins of the leg, Arch. Int. Med., 1941, lxviii, 1–17.
5. Conference on Therapy: Use and abuse of bed rest, New York State Jr. Med., 1944, xliv, 724.

6. a. HARRISON, T. R.: Abuse of rest as a therapeutic measure for patients with cardiovascular disease, Jr. Am. Med. Assoc., 1944, cxxv, 1075–1077.
b. DOCK, W.: The evil sequelae of complete bed rest, Jr. Am. Med. Assoc., 1944, cxxv, 1083–1085.
7. QUICK, A. J., STANLEY-BROWN, M., and BANCROFT, F. W.: A study of the coagulation defect in hemophilia and in jaundice, Am. Jr. Med. Sci., 1935, cxc, 501–511.
8. CAMPBELL, H. A., SMITH, W. K., ROBERTS, W. L., and LINK, K. P.: Studies on the hemorrhagic sweet clover disease. II. The bioassay of hemorrhagic concentrates by following the prothrombin level in the plasma of rabbit's blood, Jr. Biol. Chem., 1941, cxxxviii, 1–20.
9. SHAPIRO, S., SHERWIN, B., REDISH, M., and CAMPBELL, H. A.: Prothrombin estimation: a procedure and clinical interpretations, Proc. Soc. Exper. Biol. and Med., 1942, l, 85–89.
10. SHAPIRO, S.: Hyperprothrombinemia, a premonitory sign of thrombo-embolization, Exper. Med. and Surg., 1944, ii, 103–109.
11. QUICK, A. J.: The coagulation defect in sweet clover disease and in the hemorrhagic chick disease of dietary origin, Am. Jr. Physiol., 1937, cxviii, 260–271.
12. BRAMBEL, C. E., and LOKER, F. T.: Significance of variations of prothrombin activity of dilute plasma, Proc. Soc. Exper. Biol. and Med., 1943, liii, 218–220.
13. WERCH, S. C.: Reduction of coagulation time of rabbit's blood by digitalis, Quart. Bull. Northwest. Univ. Med. School, 1943, xvii, 50–51.
14. MACHT, D. I.: Experimental studies on heparin and its influence on toxicity of digitaloids, congo red, cobra venom and other drugs, Ann. Int. Med., 1943, xviii, 772–779.
15. DE TAKATS, G., TRUMP, R. A., and GILBERT, N. C.: The effect of digitalis on the clotting mechanism, Jr. Am. Med. Assoc., 1944, cxxv, 840–845.
16. MASSIE, E., STILLERMAN, H., WRIGHT, C., and MINNICK, V.: Effect of administration of digitalis on coagulability of human blood, Arch. Int. Med., 1944, lxxiv, 172.
17. WHITE, P. D.: Pulmonary embolism and heart disease; review of 20 years of personal experience, Am. Jr. Med. Sci., 1940, cc, 577–581.
18. HOMANS, J.: Pulmonary embolism due to quiet venous thrombosis and simulating cardiac and pulmonary disease, New England Jr. Med., 1943, ccxxix, 309–314.
19. a. SMITH, H. P., WARNER, E. D., and BRINKHOUS, K. M.: Prothrombin deficiency and the bleeding tendency in liver injury (chloroform intoxication), Jr. Exper. Med., 1937, lxvi, 801–811.
b. WARNER, E. D.: Plasma prothrombin: effect of partial hepatectomy, Jr. Exper. Med., 1938, lxviii, 831–835.
c. WARREN, R., and RHOADS, J. E.: Hepatic origin of the plasma prothrombin. Observations after total hepatectomy in the dog, Am. Jr. Med. Sci., 1939, cxcviii, 193–197.
d. ANDRUS, W. D., LORD, J. W., and MOORE, R. A.: Effect of hepatectomy on the plasma prothrombin and the utilization of vitamin K, Surg., 1939, vi, 899–900.
20. a. JOLLIFFE, N.: Liver function in congestive failure, Jr. Clin. Invest., 1930, viii, 419–433.
b. CANTAROW, A.: Studies of hepatic function. II. In portal cirrhosis and congestive heart failure, Arch. Int. Med., 1935, lvi, 521–529.
21. SHAPIRO, S., SHERWIN, B., and GORDIMER, H.: The platelet count and the prothrombin time after surgical operations. A simple method for detecting reductions and elevations of the prothrombin concentration (or activity) of the blood plasma, Ann. Surg., 1942, cxvi, 175–183.
22. SHAPIRO, S., and SHERWIN, B.: Studies in thrombo-embolization II: Observations on the use of Dicumarol (3, 3′ Methylene-bis (4-Hydroxycoumarin)) in embolization. Report of five cases, New York State Jr. Med., 1943, xliii, 45–52.
23. a. NORRIS, R. F., and BENNETT, M. C.: Plasma prothrombin values of mothers and infants at delivery, Surg., Gynec., and Obst., 1941, lxxii, 758–763.

b. FIELD, J. B., OVERMAN, R. S., and BAUMANN, C. A.: Prothrombin activity during pregnancy and lactation, Am. Jr. Physiol., 1942, cxxxvii, 509–514.

24. SHAPIRO, S., ROSS, V., and MOORE, D. H.: A viscous protein obtained in large amount from the serum of a patient with multiple myeloma, Jr. Clin. Invest., 1943, xxii, 137–142.

25. WARNER, E. D., BRINKHOUS, K. M., and SMITH, H. P.: The prothrombin conversion rate in various species, Proc. Soc. Exper. Biol. and Med., 1939, xl, 197–200.

26. WILSON, S. J.: Qualitative and quantitative studies on the antithrombic activity of blood serum and plasma, Am. Jr. Clin. Path., 1944, xiv, 307–315.

27. FRIEDBERG, C. K., and HORN, H.: Acute myocardial infarction not due to coronary artery occlusion, Jr. Am. Med. Assoc., 1939, cxii, 1675–1679.

28. HORN, H., DACK, S., and FRIEDBERG, C. K.: Cardiac sequelae of embolism of the pulmonary artery, Arch. Int. Med., 1939, lxiv, 296–321.

29. CURRENS, J., and BARNES, A. R.: The heart in pulmonary embolism, Arch. Int. Med., 1943, lxxi, 325–344.

30. a. ALLEN, E. V., BARKER, N. W., and WAUGH, J. M.: A preparation from spoiled sweet clover which prolongs coagulation and prothrombin time of the blood, Jr. Am. Med. Assoc., 1942, cxx, 1009–1015.

b. WRIGHT, I. S., and PRANDONI, A.: The dicoumarin 3, 3′ methylene-bis-(4-hydroxycoumarin): its pharmacologic and therapeutic action in man, Jr. Am. Med. Assoc., 1942, cxx, 1015–1021.

c. BUTSCH, W. L., and STEWART, J. D.: Clinical experiences with dicoumarin, Jr. Am. Med. Assoc., 1942, cxx, 1025–1026.

31. CROMER, H. E., JR., and BARKER, N. W.: The effect of large doses of menadione bisulfite (synthetic vitamin K) on excessive hypoprothrombinemia induced by dicumarol, Proc. Staff Meet. Mayo Clin., 1944, xix, 217–224.

32. SOLANDT, D. Y., and BEST, C. H.: Heparin and coronary thrombosis in experimental animals, Lancet, 1938, ii, 130–132.

33. DALE, D. U., and JAQUES, L. B.: The prevention of experimental thrombosis by dicoumarin, Canad. Med. Assoc. Jr., 1942, xlvi, 546–548.

34. BLUMER, G.: The importance of embolism as a complication of cardiac infarction, Ann. Int. Med., 1937, xi, 499–504.

35. SOLANDT, D. Y., NASSIM, R., and BEST, C. H.: Production and prevention of cardiac mural thrombosis in dogs, Lancet, 1939, ii, 592–595.

36. MALLORY, G. K., WHITE, P. D., and SALCEDO-SALGAR, J.: The speed of healing of myocardial infarction, Am. Heart Jr., 1939, xviii, 647–671.

37. a. BARKER, N. W., ALLEN, E. V., and WAUGH, J. M.: Use of dicumarol in prevention of postoperative thrombophlebitis and pulmonary embolism, Proc. Staff Meet., Mayo Clin., 1943, xviii, 102–107.

b. EVANS, J. A.: Dicumarol therapy in thrombotic emergencies, New England Jr. Med., 1944, ccxxx, 131–135.

38. HOMANS, J.: Deep quiet venous thrombosis in the lower limb, Surg., Gynec., and Obst., 1944, lxxix, 70–82.

THE POSTMORTEM EXAMINATION IN CASES OF SUSPECTED HOMICIDE *

By MILTON HELPERN, M.D.,† *New York, N. Y.*

THE postmortem examination in cases of suspected homicide represents one of the most important applications of medicolegal science to the needs of the community. Its proper performance is of paramount concern to those agencies of government responsible for law enforcement and the effective administration of justice. In view of the desire of the medical and legal professions, increasingly evident in recent years, to improve the standards and quality of medicolegal practice throughout the country, it was considered timely and appropriate again to review the subject of the postmortem examination in cases of homicide, and to point out what is expected in the way of performance of the person entrusted with it. In a paper published several years ago, the author described and discussed the routine procedures necessary in such examinations.[1]

INADEQUACIES OF MEDICOLEGAL AGENCIES AND OF THE STATUTES PERTAINING TO THEM

At present, in most sections of the country, the postmortem investigation of homicide is inexpertly and inadequately carried out. The chief reasons for this unsatisfactory performance are to be found in the faulty organization of official medicolegal agencies responsible for such investigation and in the lack of uniformity of statute laws which have established such agencies, and defined and limited their functions. The deficiencies inherent in governmental medicolegal departments have discouraged able physicians from specializing in legal medicine, thus permitting the practice of such an important specialty to fall into the hands of untrained and unqualified medical persons. Legal medicine, as a specialized branch of medical science, has not kept pace with the progress made during recent years by the other specialties. There are only a few places in the country where it is practiced by trained specialists, and it is therefore not surprising that the postmortem examination in homicide cases is performed haphazardly and unsatisfactorily by untrained and inexperienced physicians. As long as the inadequate medicolegal systems now in force throughout the country are permitted to

* Received for publication January 18, 1946.

† Deputy Chief Medical Examiner, Office of the Chief Medical Examiner, City of New York.

In April 1943, the Annals of Internal Medicine published a series of articles dealing with subjects of joint interest to the medical and legal professions, as part of a symposium which was published in various medical and legal journals. This was prepared under the editorial supervision of Hubert Winston Smith, M.D., now Professor of Legal Medicine at the University of Illinois, Urbana, Ill. This article is one of a continuation of that series. An index of the entire series may be obtained from Dr. H. W. Smith at cost (20 cents).

continue, the unsuspected homicide will escape detection and the obvious one will be inexpertly and improperly handled medically.

An examination of the statute laws pertaining to coroners and to medical examiners in the United States [2] reveals that, in most jurisdictions where the office of coroner exists, and also in some of the comparatively few localities where there is a medical examiner's system, the statutes provide only for the investigation of obviously violent and suspicious deaths. There does not appear to be any recognition of or provision for the important fact, so well known in medicolegal experience, that in many violent deaths there are not any externally obvious or suspicious signs of violence on the body of the deceased. Since the statutes in most instances do not provide for the routine official investigation of such cases, certain unsuspected homicidal and other types of violent death, not outwardly obvious or suspicious, necessarily escape detection.

In two States, namely Massachusetts and Rhode Island, where there is a medical examiner's system, permission for a medicolegal autopsy, which the medical examiner deems necessary, must first be obtained from some other authority, usually the prosecuting attorney, who is in a position to refuse such permission or to question the necessity for the autopsy. In those jurisdictions where there is a coroner, that official, even though not a physician, can decide whether or not a postmortem examination is necessary.

Desirable Features of Medical Examiner's System in New York City, Essex County (New Jersey) and Nassau County (New York), and the State of Maryland

The coroner's office in New York City was abolished and a medical examiner's office established in its place by an act of the State Legislature passed in 1915.[3] The law went into effect in 1918. A similar medical examiner's system was instituted in Essex County, New Jersey, which includes the City of Newark, in 1927, and in Nassau County, New York, in 1938, and in the entire state of Maryland in 1939, by statutes almost identical with that which created the medical examiner's office in New York City. In these four jurisdictions, the medical examiner's office functions entirely independently of other official agencies, and the responsibility for the entire medicolegal investigation rests with a trained medical personnel. The investigations of the medical examiners are in no way controlled or hindered by any other agency. In these four offices, the law [4] requires that all sudden, suspicious, unusual, and violent deaths, and deaths where there has not been any physician in attendance, must be reported to the medical examiner's office for investigation by a medical examiner, no matter how seemingly unsuspicious the death may be. It is only by the routine investigation of this great variety of deaths, that unsuspected homicides are discovered.

Other medicolegal systems concerned only with obviously violent and

suspicious deaths permit certain unsuspected, not obviously violent homicidal cases to pass undetected. This is a fundamental defect in the medicolegal systems of most jurisdictions in the United States. This defect cannot be corrected merely by improving the quality and training of the medical personnel, but it will continue until the statutes are altered to require the prompt investigation from the very beginning, by trained medical examiners, of all sudden and unusual as well as suspicious and violent deaths.

Lay persons, whether private citizens, police officers, prosecuting attorneys, coroners, or physicians not trained to carry out medicolegal investigations, cannot decide the nature of sudden death or of death where there has not been any medical attention, and they should not be burdened with that responsibility. Their opinion of any such death should not preclude an investigation by a medical examiner with the authority to decide upon the advisability and necessity of autopsy, and to perform such autopsy. The practice in most communities of referring only the obviously violent and suspicious cases to the medicolegal department for investigation is responsible for the too frequent embalming and burial of bodies, necessitating their subsequent exhumation for autopsy, because violence not being apparent was not suspected at the time of death. It follows that a certain number of cases of unsuspected homicide remain buried and are never discovered, and it is not an exaggeration to say that a subtle murder may go uninvestigated and undiscovered.

In New York City, of a total of about 75,000 deaths each year, from 15,000 to 16,000, or roughly 20 per cent, are referred to the Office of the Chief Medical Examiner for routine investigation [5] because of the medical examiner's law. Of the referred cases, about 5,000 or one-third are violent deaths, and of these, about 350 are homicidal. Thus, homicides constitute approximately 2 per cent of the total number of deaths investigated each year.

A number of violent deaths, including some which are homicidal, are detected each year only by careful routine postmortem investigation, the cases having first been reported to the Medical Examiner's Office as nonsuspicious. Such cases would not have been investigated and autopsied and would have escaped detection in those jurisdictions where only obviously violent and suspicious deaths are reported to the authorities. If unsuspected violent deaths and homicides are to be detected, all sudden, unexpected and unusual deaths must be investigated routinely by an official medicolegal agency.

Qualifications of Physician Performing Examination

In every homicide and in every death where there is the slightest suspicion of homicide, a postmortem examination including a complete and accurate autopsy should be performed on the body of the deceased by a qualified and authorized physician. The person entrusted with this examination should be a pathologist trained in that branch of legal medicine called

forensic pathology and working in the official capacity of a medical examiner or coroner's physician. There should be adequate facilities at his disposal for the performance of an autopsy and for any other investigation along histological, chemical, bacteriological and serological lines which are indicated by the nature of the case. The fallacious idea exists in the minds of many of the laity and some of the medical profession that any physician, because of eminent qualification in some other branch of medicine, or any pathologist without medicolegal training, is qualified to carry out this special type of postmortem investigation.

Careless Performance and Misinterpretation of Autopsy

In many cases of homicide, the inadequate postmortem examination by an incompetent or unqualified physician has been followed by a grossly erroneous interpretation of the findings. Many homicidal deaths have escaped detection because of the failure on the part of an inexperienced and careless investigator to recognize the more subtle anatomic evidences of criminal violence.

In obvious cases of homicide, in which only superficial postmortem examinations were thought necessary, the lack of detailed medical information has seriously handicapped the work of law-enforcement agencies. Thus, the police have been deprived of valuable clues which the complete postmortem examination would have revealed, and they have been hampered in their attempts to solve the crime. In other instances where a perpetrator has been apprehended and brought to trial, the prosecuting attorney has found himself at a serious disadvantage because of the lack of complete medical evidence necessary for the proper establishment of the corpus delicti.

There have also been deaths from purely natural causes which because of the circumstances were misinterpreted and attributed to homicidal violence, with the subsequent prosecution and conviction of an accused innocent person for a non-existent crime. The failure to understand the anatomic findings in a postmortem examination, and their misinterpretation, have not infrequently resulted in flagrant miscarriages of justice. Thus, artefacts, some produced by the embalmer, also normal findings, natural disease processes and accidental and suicidal injuries have been erroneously considered evidence of homicidal violence.

The writer is aware of a case in which it was alleged that the deceased died after having been struck on the head with a slipper. After an incomplete autopsy limited to the head of the embalmed body, a medical opinion was arrived at and testified to that death had resulted from the blow to the head. The brief autopsy report did not disclose any pathologic changes in the skull or brain attributable to trauma. The cause of death was certainly not determined since the body was not opened nor was any chemical examination made of the brain for the presence of alcohol. This chemical test was precluded because the body had been embalmed before the incomplete autopsy

was performed. Nevertheless, the accused person was convicted of homicide which was not proved medically.

Postmortem Examination Commences at Scene

The scope of the postmortem examination in a frank or suspected case of homicide extends beyond the mere determination of the cause of death and the means by which it was brought about. In homicidal cases where the deceased is found dead, the postmortem examination properly commences with a careful study by the medical examiner of the undisturbed dead body at the place where it was discovered. This scene may or may not be the place where death occurred and it is not necessarily the place where the violence which caused the death was inflicted.

Thus, the undisturbed dead body of a woman was found on the sidewalk at 2 o'clock in the morning. The circumstances under which it was found and the examination of the body revealed that it had been dead for some time and moved after death. Rigor mortis had disappeared and there were postmortem lividities on the front of the body as well as on the back. Death had been caused by strangulation. The solution of this case is described on page 694 under the topical heading of Routine Blood Grouping Determinations.

In another case, the deceased was stabbed while on the street and then ran across the roadway, up two flights of stairs into his apartment where he locked himself in the bathroom and died. When examined by the police and the medical examiner, the undisturbed dead body was found seated on the toilet. The cause of death was a stab wound through the heart.

It is extremely important to learn the circumstances surrounding the death. Although it is true that in the majority of homicides, even a superficial postmortem examination will establish the homicidal nature of the death, there are certain types of homicide in which the evidences of violence are superficially lacking and it is only the careful study of the undisturbed body at the scene and the circumstances surrounding the case, which arouse suspicion that the death may be homicidal. Such a body removed from the scene may show nothing externally to suggest a violent death and thus might escape the close scrutiny and careful necropsy which would certainly be indicated if it were examined in its original surroundings by a trained medical observer. The practice required by law in the City of New York of having a medical examiner visit all dead bodies at the places where they are found has minimized the possibility of the unsuspected homicide passing unnoticed.

The types of homicide which may readily escape suspicion and detection if the scenes are not visited include deaths from manual and ligature strangulation, smothering, carbon monoxide poisoning, certain deaths caused by concealed stab wounds and bullet wounds and also some deaths from criminal abortion.

There are many cases in which a complete and careful necropsy indicates that death resulted from violence, but cannot establish that the death was necessarily by homicidal means. The necropsy findings in certain cases of drowning, carbon monoxide and other types of poisoning, blunt force injuries, especially those resulting from falls from a height, may be consistent with homicidal, suicidal or accidental death. Only a careful investigation of the circumstances surrounding the death will enable the medical examiner to classify the case correctly. The classification of a certain number of violent deaths must remain undetermined. This is especially true of drowning cases, in which the bodies are recovered after long periods of submersion, and cases of poisoning in which the clinical course was of long duration and the diagnosis unrecognized during life.

Experience with the many ordinary and bizarre forms of violent death is of the greatest value to the medical examiner in helping him decide the homicidal, suicidal or accidental nature of any given case. The experienced observer is quick to recognize the suicide which has been tampered with in the attempt to create the impression of a homicide, usually for purposes of collecting insurance, or the homicidal case which has been altered to make it resemble a suicidal, accidental or natural death.

Examples

Many examples [6] can be given to illustrate the importance of the examination of the body at the scene by the medical examiner in helping to determine the homicidal, suicidal or accidental nature of a violent death.

The body of a young negress was discovered at the foot of a long flight of stairs, lying on its back, the head resting on the first step, the legs sharply flexed under the thighs. The handle and part of the blade of a new, long, single-bladed jack knife were plainly visible protruding from a fatal stab wound of the chest. At necropsy, the point of the knife was found to have penetrated an intercostal space, the pericardium and the pulmonary artery, death having resulted from an intrapericardial hemorrhage.

The unusual position of the body and the weapon at first aroused the suspicion of homicide but investigation at the scene disclosed that the deceased had purchased the knife on the previous day, and that a short time before her death, had visited her estranged husband who was living in the apartment at the top of the stairs. After an unsuccessful attempt to effect a reconciliation, the deceased left the apartment in a depressed mental state mumbling something as she passed through the door. On the landing outside the door, she was seen to slump to her knees. The witness who saw this ran back into the apartment for help but when she returned to the landing, the deceased had already staggered or slid down the full length of the flight of steps to the place where her body was discovered. Her purse and several drops of blood were found on the tiled floor of the upper landing near the apartment door. The necropsy revealed that the track of the stab wound was a short one and could readily have been self-inflicted with the use of slight force. Needless to say, the husband and others in the apartment were subjected to a thorough questioning, and it was learned from them and from other reliable sources that the deceased had been despondent and had threatened suicide.

In another case a suicidal shooting at first had aroused suspicion of homicide. The body of the deceased scantily clad was found lying on the bed. There was a contact

bullet wound of entrance above the left breast, and a corresponding exit wound on the back of the left side of the chest. The bullet was found embedded in the wall behind the bed. A revolver was found near the edge of the bed under the right hand of the deceased, but it had evidently been tampered with after the shooting, by someone who removed the discharged cartridge shell from the cylinder chamber and substituted for it a single, undischarged cartridge. There was reason to believe that this had been done by the common-law husband who owned the pistol and who ignorantly believed that the substitution would remove any suspicion that he might have shot the deceased. Fortunately, the case was clarified by a suicide note in the deceased's handwriting.

In another case[7] investigated by Dr. Morgan Vance, the homicidal character of a smothering was suggested to him by the position of the undisturbed dead body of a young woman sprawled out in a prone position on the bed with the face buried in a pillow. There were no external or other evidences of injury, only the signs of asphyxia. The male companion of the victim was apprehended and confessed that he smothered her while trying to stifle her screams. If the medical examiner who performed the autopsy had not first examined the body at the scene the homicidal character of the death could not have been established nor would it have been suggested from the autopsy alone.

Procedure in Suspicious Deaths

When a dead body is discovered in New York City, and the indications definitely point to homicide or are suspicious of homicide, the police who are the first in authority to arrive at the scene, immediately notify the Office of the Chief Medical Examiner of the death and a medical examiner is promptly dispatched to the scene of the death. Such cases take precedence over non-suspicious deaths. In regard to the latter, it has already been emphasized that an apparently non-suspicious death may be homicidal. It therefore behooves the medical examiner to be on the alert in the investigation of every case if the unsuspected homicide is to be discovered.

There must be no delay in the visit of the medical examiner to the scene, no matter what time of the day or night the case is discovered. The body and its surroundings may not be disturbed until after the medical examiner has arrived and completed his preliminary investigation.

The preliminary examination by the medical examiner is carried out in coöperation with members of the Police Department including detectives especially trained for the investigation of homicidal cases. In addition to the experience which these detectives receive in the field, handling the many cases assigned to them, the New York City Police Academy for many years has conducted systematic courses for detectives in which they are taught the essentials of the medical indications of crime. These courses are given by members of the medical staff of the Office of the Chief Medical Examiner who utilize for the purpose a very extensive collection of lantern slides, illustrating actual cases of the ordinary and extraordinary types of homicidal, suicidal and accidental death. Significant details revealed by the study of the dead body at the scene are especially emphasized in these courses. Needless to say, this teaching has been enthusiastically received and has proved most valuable in bringing about an intelligent and sympathetic coöperation

between members of the Police Department and the medical examiners in their investigations of violent deaths.

Independent Character of Medical Examiner's Investigation

The medical examiner conducts his investigation independently of other law enforcement agencies. His functions do not fall under the jurisdiction of the police authorities or prosecuting agencies. Nevertheless, he coöperates fully with these other departments, informing them of the probable nature of the case, offering useful suggestions and supplying them with whatever information is revealed by his examination at the scene and by the subsequent necropsy. He should be entirely unbiased in his study of any case and must not venture any opinion which he cannot justify by the findings in his examination. He must bear in mind that he is an investigator and not a prosecutor and if his investigation clearly discloses that there are no medical indications of crime in a suspicious or a violent death, or that the findings are not necessarily indicative of homicidal violence, he must be prepared to give such an opinion. If the medical findings definitely point to criminality, the examiner must be firm in his opinion even though the outward appearance of the case at first did not suggest such a possibility.

Steps in Investigation at Scene

Upon his arrival at the scene of a suspicious or frankly homicidal death, the medical examiner records the time and place of his arrival and examination, and inquires into the circumstances under which the body was found. He determines how, when and by whom the body was first discovered and if possible by whom and when the deceased was last seen alive. He obtains the name and shield number of the first police officer, usually a patrolman, to arrive at the scene and a statement from him as to the time he was notified about the finding of the body, the name of the person who notified him and the time he first saw the body.

The medical examiner also inquires of the patrolman or of the first person who found the body as to its original position and whether or not the body had been moved from its original position after it was found. Such might be the case if the deceased was still alive or thought to have been alive when first discovered. Any attempts at resuscitation necessitating movement of the body, disarrangement of the clothing, the application of tourniquets, bandages or towels to bleeding wounds, should be recorded, also the name of any ambulance surgeon who might have treated or moved the deceased or pronounced him dead.

In cases where attempts at resuscitation have been made, the medical examiner should instruct the patrolman and the ambulance surgeon to record promptly and fully the original condition and position of the deceased when first seen by them. Frequently hospital surgeons called upon to treat wounded persons, have neglected to describe accurately the patient's wounds, omitting mention of their exact nature, number, size and location.

In many homicidal cases, not immediately fatal, the descriptions of the wounds in the hospital records are inadequate. It must be remembered that the original appearance of a fatal wound may be obliterated by a surgical operation, performed in the attempt to save the patient's life. Should the patient die later, the medical examiner may be unable to recognize and describe the characteristics of the original wound. This information can be furnished only by the surgeon who first saw and treated the patient. It is therefore important that every surgeon should be familiar with the detailed characteristics of penetrating and non-penetrating wounds, which might result from homicidal violence. There is a regrettable lack of interest and knowledge among many practising physicians and surgeons concerning the interpretation and recognition of the various types of bullet and stab wounds, lacerated wounds and blunt-force injuries which they may be called upon to treat, and about which they may be called later to testify in a criminal action. Through carelessness or ignorance, many important details of wounds are overlooked, details which may have considerable medicolegal importance in subsequent criminal proceedings.

Identification of Body by Police Officer

The body of the deceased with its clothing is identified to the medical examiner by the first patrolman who saw it. If such identification is not made at the scene, the police officer must report to the mortuary and there identify the body and clothing to the medical examiner. The identification by the police officer is necessary in every homicidal case and especially in those cases in which the deceased did not die immediately but survived for a variable period of time in a hospital, for in such instances the medical examiner would not have seen the deceased at the scene of the crime. The police identification is an indispensable link in the chain of evidence necessary to connect the dead body, autopsied by the medical examiner, with the particular crime of which the perpetrator is accused.

The time and place of the police identification must be carefully recorded. It is not sufficient for the patrolman simply to come to the morgue and look at the dead body; he must identify it to the medical examiner or to some other available and responsible person who in turn will see or has seen the body in the presence of the medical examiner handling the case. Whenever possible, it is also advisable to have the identification made to any other medical examiners present at the autopsy. This identification to another medical examiner will enable him to testify to the autopsy findings and cause of death in the event of the enforced absence from the trial of the medical examiner who performed the autopsy.

Photographing the Scene

Prior to the handling of the body and before disturbing any of the surroundings at the scene, as many photographs should be taken as are necessary

to show all the details. These photographs are best taken by a Police Department photographer equipped with a view camera having a wide-angle lens and capable of taking a fairly large size, usually an 8 by 10 inch, picture. Photo-flash bulbs are used as a source of illumination, permitting the photographs to be taken in any kind of light. The medical examiner may also take photographs and should make a diagrammatic sketch of the scene, indicating the size and shape of the room, the arrangement of the furniture, doors and windows and the position and location of the body, blood stains, weapons, discharged bullets and cartridge shells, also any other noteworthy findings.

Signs of Death

He then proceeds to an examination of the body, paying particular attention to the signs of death.[8] He carefully notes and records the extent of rigor mortis, the degree of cooling of the body and in this connection the amount of clothing or covering on the body and the temperature of the room. The color, location and amount of the postmortem suggillations or lividity and the presence of any other postmortem changes, such as putrefaction, mummification, adipocere formation, and destructive marks on the body, caused by insects, such as ants, and blowfly larvae, or by rodents and larger animals, should be noted; also any attempts at dismemberment and disposal of the body. Putrefactive changes and postmortem mutilations by animals should not be confused with antemortem wounds.

The careful study of the signs of death enables the trained investigator to form some estimate of the probable postmortem interval. Such estimates are the more accurate, the shorter the interval. At best, only a guarded opinion should be given concerning the postmortem interval, because the onset, progress and duration of rigor mortis and the rate of cooling of the dead body may show great variation, being dependent upon many factors.

The position of the body with reference to the location and color of the suggillations is of great importance in determining whether or not the body has been moved after death. In this connection, it must be realized that if the body is moved immediately after death, before the suggillations have appeared, such movement will not be detected by a study of the lividity when the body is found. Estimates as to the probable postmortem interval can only be made if the body is visited at the scene, and are impossible if it is examined for the first time on the following day, after it has been moved and chilled in the refrigerator over night. Reliable information as to the probable postmortem interval is of considerable value to the police in their investigations and in their attempts to trace the movements of the deceased prior to death, and to check any alibis which may be offered by a suspected perpetrator.

The color of the postmortem suggillations is significant to the trained medical observer in that it may reveal the cause of death. The cherry red

color of the lividity in carbon monoxide poisoning is easily recognized. It is also important not to mistake deep blue suggillations for antemortem bruises, an error which the inexperienced observer may make.

Preliminary Examination for Wounds

The body is then examined for obvious wounds but a final opinion as to their exact nature and number should not be ventured on the basis of this preliminary examination at the scene. The nature of many wounds is self-evident. In shooting cases, it is helpful to the police if, in addition to the entrance wounds, obvious exit wounds are found with corresponding holes of exit of bullets in the clothing. A search of the premises may then reveal a bullet. In some instances, a bullet, in passing through the body, may carry with it a strand of hair or a fragment of bone or soft tissue. At times, a bullet may be felt just beneath the skin and may be easily removed by a small skin incision. The character and calibre of such a bullet may show whether it was fired from a revolver or automatic pistol. If fired from the latter type of weapon, an ejected cartridge shell should be searched for and if found would indicate that the deceased had probably been shot at the place where the body was found.

The detailed examination of bullet and knife wounds is best made at the time of the necropsy, when the wounds can be carefully washed and studied. The presence of considerable extravasated blood may obscure their finer details at the scene. In assaults with blunt weapons, the pattern and extent of a wound may suggest the type of weapon that should be sought for by the police, but again the finer detail of the pattern will be more readily detected at the necropsy, after the surface of the wound is cleansed of blood and other material which may obscure it.

The hands of the deceased should be carefully examined for the presence of defense wounds, powder burns and residues, blood stains, various objects such as strands of cloth and hair and fragments under the finger nails.

Collection and Preservation of Evidential Material

It is the responsibility of the medical examiner to preserve all objects found on or in the body of the deceased, which may have anything to do with the cause of death, or which may furnish clues useful in the apprehension and conviction of the assailant. Thus, the clothing of the deceased, strands of hair, cloth fragments, bullets, slugs, broken-off knife blades, or other penetrating weapons, blood stains and stains of body discharges such as semen should be carefully preserved. Small loose objects which might be lost during the transfer of the body from the scene to the morgue, should be carefully preserved in labelled containers for subsequent study.

In one interesting case, the deceased was found lying dead on the roof of a tenement house, with a bullet wound through the head. A button and a torn piece of fabric to which it was attached, were found in the clenched

hand of the victim. These articles were quietly removed by the police officer, who subsequently made it his business to attend the wake which was held over the body of the deceased. One of the visitors to the wake, who came ostensibly to mourn, was observed by the police officer to be wearing an overcoat of the very same fabric as that found in the hand of the deceased and with a button missing, which had evidently been torn out. He was arrested by the police officer and when confronted with the button and fabric found in the hand of the deceased, which fitted exactly the torn area in his overcoat, confessed the murder.

In another case the body of an elderly woman who had been murdered was found in the rear of her small delicatessen store. The victim's throat had been cut deeply in several places. There were defense cuts on one hand and other evidences of a struggle. Several strands of hair were found in the hands of the deceased and removed by the medical examiner at the scene for examination later. All but one of these hairs were long and gray and similar to those on the victim's head. A single short dark brown hair was also found which microscopically was similar in color and in cross section to the scalp hairs of the assailant who was taken into custody later and confessed the crime.

The medical examiner also supervises and directs the preservation of implements, utensils, weapons, wearing apparel, furnishings, suspicious stains, blood stains, body discharges, food, drink, medicines and chemicals, which he thinks may have some bearing on the case. All such objects should be carefully labelled and wrapped for delivery by a police officer to the laboratories of the toxicologist, the serologist, or to the technical laboratory of the Police Department, for whatever examinations may be indicated. In handling and collecting such material, precautions must be taken not to mar fingerprints or to add fingerprints on weapons and smooth-surfaced objects. Firearms, bullets and cartridge shells, found at the scene, are gathered up by the police, examined for fingerprints and then removed for study and tests by ballistics experts.

After the medical examiner has completed his preliminary examination and has reduced all his findings to writing in a report as required by law, the police officer in charge of the case searches the clothing of the deceased for personal belongings, and subsequently delivers them to the custody of the property clerk at Police Headquarters. The personal belongings frequently reveal the identity, the occupation, habits and associations of the deceased.

If the identity of the deceased is unknown and there is reason to believe that he has a criminal record, finger prints may be taken at the scene for purposes of identification, but not until the medical examiner has had an opportunity to examine the body. Finger printing of the deceased at the scene should not be done in cases that may require an examination of the finger nail scrapings. Examination of such scrapings is indicated in cases of assault in which the victim may have struggled with and scratched the

assailant. Fragments of skin, hairs, cloth fibers, blood and other substances which may prove important as clues and as evidence may be obtained in this way. It is better procedure, if the deceased is known, to postpone finger-printing until after the external examination of the body has been completed by the medical examiner at the time of the necropsy. Finger prints of the deceased, however, should be taken in every homicide.

The medical examiner then orders the removal of the body to the mortuary for necropsy. Care must be exercised during the transportation of the body, that it is not mutilated and that nothing is done to interfere with the anatomical lesions which are present on the surface. Rough handling of the dead body may produce confusing postmortem injuries. The clothing of the deceased, which must be carefully described in connection with the necropsy, must not be destroyed or unnecessarily soiled with extraneous dirt or with the body discharges of the deceased. A police identification tag filled out at the scene by the patrolman assigned to the case is sent along with the body.

Necropsy

In a homicidal case, the necropsy should be performed as promptly as possible, preferably by the medical examiner who saw the body and investigated the case at the scene where it was found. Whenever possible, the necropsy should be witnessed by another medical examiner, and this fact should be noted in the protocol.

Police and Personal Identification of Body to Medical Examiner. Finger Printing of Deceased

In addition to the police identification, which has already been discussed, the identity of the deceased is established by his relatives or friends, who must also identify the body to the medical examiner who performs or who has witnessed the necropsy. The personal identification must be sworn to in an affidavit by the person who makes it. Mistakes in identification both deliberate and unintentional have been made and should be guarded against. The persons making the identification should be questioned carefully as to their relationship to the deceased, the duration of their acquaintanceship, and the last time and the circumstances under which they saw the deceased alive. In doubtful cases, the person making the identification should be required to state the physical characteristics of the deceased including any distinguishing marks, deformities and scars on the body. A deliberate false identification of a dead body is a misdemeanor and is punishable by law.

Whenever possible, more than one personal identification should be taken and preferably by persons who will be available to testify, should the case come to trial. Identification by persons living in distant cities may create difficulties for the prosecuting attorney, should he find it necessary to subpoena them as identifying witnesses at the trial.

Finger prints are taken routinely by the Bureau of Identification of the Police Department of all persons who die by homicide. Such prints frequently prove valuable in helping to establish the identity and also the criminal record, if any, of a deceased person. The finger prints are also useful for comparison with finger impressions found at the scene. In this connection it would be helpful to have on file the finger prints of the medical examiner who may unwittingly deposit finger prints during his investigation at the scene.

Body Should Not Be Embalmed Before Necropsy

Under no circumstances should the body be embalmed before the necropsy, as the embalming process vitiates many chemical tests which may subsequently be found necessary. The formaldehyde in the embalming fluid renders the detection of alcohol and cyanide in the organs difficult if not impossible. Besides interfering with the proper toxicological examination of the organs, embalming also produces confusing artefacts in the body. The trocar punctures throughout the thorax and abdomen may cause considerable mutilation of the various organs and make difficult the interpretation of blunt force injuries of the hollow and solid organs and also the tracing of the exact course of a penetrating wound.

It is only when a body has to be exhumed for a belated necropsy not originally performed because homicide was not suspected, that embalming has proved useful because of its preservative effect on the tissues. The necropsy on an exhumed embalmed body has all the limitations of one performed on a freshly embalmed body. In addition the postmortem decomposition may be considerable despite the embalming.

Recording of Findings During Progress of Necropsy

A well equipped necropsy room should be available, with good light and necessary instruments for the performance of the necropsy, which should be done carefully and completely. During the progress of the necropsy, the positive and also the negative findings are dictated to a stenographer. The inclusion of significant negative findings in the record indicates that the necropsy was performed understandingly and thoroughly. The value of carefully recording the negative findings in the necropsy is appreciated readily by any medicolegal pathologist who has had occasion to testify in court under cross-examination. The defense counsel in a criminal action may ask the medical examiner many questions about the necropsy. If the negative findings are not mentioned in the autopsy report, the opposing counsel may succeed in his attempt to create the impression that the necropsy was carelessly done and that certain details were perhaps overlooked.

A necropsy can be performed properly only once, and one poorly performed is perhaps worse than none at all. The curious notion that it can be satisfactorily done over and over again exists in the minds of many, judging

from the frequent reports in the newspapers, of bodies inadequately examined the first time, being exhumed for a second and even a third necropsy.

External Examination of Dead Body

The dead body should be carefully undressed and the clothing carefully laid aside for examination after the necropsy. In removing the clothes, care must be taken not to obliterate any cuts or bullet perforations or to soil them unnecessarily with blood or body discharges. The body is then weighed on accurate scales provided for the purpose, and its height measured. A large pair of wooden calipers is useful for the latter purpose and also for measuring the location of wounds on the body, with reference to their distance from the heel.

The external surface of the body is examined very carefully and described in considerable detail. The sex, color, approximate age, nutritional state, the skeletal and muscular development, the color, length, amount and distribution of hair, the appearance of the corneae and conjunctivae, the color of the irides, the appearance of the nose, ears, mouth, lips, gums and teeth should all be noted.

The extent of rigor mortis, the distribution and color of the postmortem lividity, any evidences of putrefaction, mummification and adipocere formation, postmortem mutilation and dismemberment by human agencies, postmortem injuries by insects, crustacea and larger animals, and by mechanical, physical or chemical agents are carefully described; also tattoo marks, scars of old wounds, needle puncture scars of drug addiction, amputations, surgical scars, and the condition of the genitalia.

Evidence of bleeding from any of the orifices such as the nose, ears, mouth, and genitals or anus is noted; also the presence and location of any small dark blue postmortem hemorrhages known as Tardieu spots, petechial hemorrhages, purpuric spots, cyanosis or pallor of the skin or mucous membranes, subcutaneous emphysema, edema and icterus.

The hands are carefully examined and described, noting the development and the presence or absence of any wounds or unusual stains. The condition of the finger nails should be noted, and scrapings taken from under the finger nails for subsequent microscopic examination in certain cases. The size, location and condition of any surgical operation wounds are also described.

Examination and Description of Wounds

The exact location, size, character and probable age of all wounds, even the most minute, should be recorded, and the presence of any vital reaction in and about any of the wounds should be noted; thus, the changed or faded color of a contusion, and any evidence of infection or inflammation in a lacerated, incised, stab or bullet wound, would indicate that it was inflicted some time before death. Old or recent wounds may be found on the same

body, along with fresh wounds, and these must be carefully differentiated and evaluated. A microscopic examination of tissue from a recent wound will show a characteristic inflammatory reaction, not to be found in a wound inflicted just before or at the time of death.

A correct estimation of the age of a wound is often difficult and may require a careful gross and microscopic examination. It is especially important in cases of violent death in which the deceased is found dead, or dies shortly after being found, of injuries sustained previously which were not immediately fatal. In many cases of fatal blunt force injury to the head or to the abdominal viscera, death is delayed; there may be no suspicion of an injury until the necropsy is performed. If a satisfactory investigation is to be made by the police in such cases, the medical examiner must not mislead them with a careless, arbitrary and inaccurate estimate of the age of the injury. The correct estimate may exonerate some person who is being held wrongfully as a suspect and direct the police investigation along successful lines.

Photography, Drawing and Diagramming of Wounds

Wounds, especially when they are multiple or patterned, or in any way unusual, should be photographed. These photographs should reveal all the finer details of the wounds which show up best if the surrounding skin is washed clean of blood and then carefully dried. Extraneous objects should not be included in the photographs. With close-up bullet wounds, care must be taken not to wipe away powder residues too vigorously. When there is much smoke deposit on the skin, this should be photographed first and then carefully washed off to permit accurate delineation of the bullet perforation, the powder burn and the embedded powder grains. The smokeless powders now loaded into most pistol cartridges produce very little smoke deposit on the skin.

If possible the medical examiner should learn to take his own photographs and develop and print his own pictures, so that he may offer them in evidence at a subsequent criminal proceeding. If such photographs are taken or finished by a professional photographer, it will be necessary, if they are to be offered in evidence, to produce the photographer to testify that he made them. Drawings also serve a useful purpose; these may be diagrammatic. The diagrammatic representation of wounds is made easy if a large printed outline drawing of the front, back and side views of the body is available. These can easily be filled in and labelled to correspond to the description of the wounds in the protocol.

Measurements

The location of wounds should be indicated by accurate and easily interpreted measurements of their distance from common fixed landmarks on the surface of the body. It must be borne in mind that the nature and location

of wounds must be made understandable to non-medical persons; for example, to the presiding judge, the counsellors and jury at a trial. The direction and length of the track of every penetrating laceration, stab or bullet wound, and the structures and organs through which the track of such wound passes, must be recorded.

It is practical to express measurement of distance in inches, as well as in centimeters, and weight in pounds and ounces, as well as in grams. This will prove useful when testimony is subsequently given in court, when the pathological findings have to be translated to an assemblage of lay persons, who may be unfamiliar with the metric system of measurement.

What the Necropsy Must Reveal to Indicate Homicide

The unsuspected, the possible and the obvious homicide are definitely established by the necropsy, which is the most important part of the postmortem examination. The necropsy, to establish death by homicide, must reveal a cause of death consistent with such an interpretation. A wound or combination of wounds [9] of sufficient severity to produce an immediate or delayed fatal effect on the body must be demonstrated together with the effects produced. The fatal effects, or complications resulting from the wound or wounds may be shock (when the wounds are very severe), hemorrhage, asphyxia, infection, thrombosis or embolism, occurring singly or in combination. But whatever the fatal complication may be, it must be directly related to and caused by the primary wound or injury which must also be demonstrable. The fatal complication or effect is designated as the immediate cause of death. The wound or injury causing the complication is the primary cause of death. The relationship of the fatal complication to the primary wound must not be equivocal but definite, to establish that the death was caused by violence.

In a case of poisoning, the presence of poison in the body and its deleterious effects on the organs must be determined. In this connection certain poisons may be eliminated from the body before the victim dies of their deleterious effects. At necropsy, only the effects and not the poison will be found. In such cases it is important to learn whether any poison was detected in the patient during life. If it was not demonstrated in the patient, the findings at autopsy would be difficult to use as proof of poisoning in the absence of poison in the tissues.

Any natural disease process revealed by the necropsy must be evaluated as to whether it has contributed to the cause of death or has been entirely unrelated to it. Occasionally the necropsy in a suspected case of homicide will disclose that death was not caused by violent means, but entirely or in great part by natural causes. Before attributing the death to disease in the latter type of case, a complete necropsy should be performed, including an examination of the skull and brain, the organs of the neck, and the spine and spinal cord, despite the absence of any outward indications of violence to these

regions. If the necropsy does not reveal any evidence of physical violence or of obvious disease, the organs should be saved for chemical examination to determine whether or not poisoning has occurred, and pieces of tissue from the organs should be taken for histological examination to determine whether or not a disease process existed, which was not evident on gross examination.

Homicidal Asphyxiation

In many cases of homicidal asphyxiation, external signs of injury may be absent from the neck and the cause of death is revealed only after the exposure, removal and careful dissection of the organs of the throat and neck, especially the larynx, which may show evidence of injury or obstruction. In ligature strangulation and in choking, injuries of the larynx such as occur with manual strangulation are usually absent, the ligature or gag found in position on the body of the deceased together with the signs of asphyxiation indicating the nature of the case.

In smothering, the necropsy may only reveal evidence of asphyxiation, the suspicion of homicide arising from the investigation of the dead body at the scene [7] and the surrounding circumstances. In cases of manual strangulation, the grouped abrasions on the neck produced by the fingers or finger nails of the assailant are not always present, especially in cases of "mugging" in which the assailant, approaching from behind, uses his forearm to compress the victim's neck.

Fatal Wounds Without External Evidence of Trauma

Fatal wounds of the skull and brain such as penetrating stab wounds [10] and non-penetrating blunt force injuries can occur with little or no external evidence of injury. In figure 1, the small size and inconspicuous appearance of a fatal ice pick stab wound of the scalp is illustrated. The wound was originally concealed by hair. The weapon perforated the skull and brain. Injuries of the cervical spine or spinal cord may remain undetected unless the spinal canal is explored and the cord removed and examined. The application of a blunt force, such as a kick, or a blow with a stick to the abdomen, may cause a rupture or laceration of a hollow or solid viscus, without any external evidence of wounding. In several fatal shooting cases, the bullet perforated the orbit between the open eyelids. With the eyelids closed, the wound was not evident. In two of these the bullet passed through the inner canthus of the eye medial to the eyeball. In a third case, the bullet perforated a spectacle lens and then passed through the eyeball. When this body was found lying prone on the ground, the eye wound was not recognized and it was first thought that the deceased had died of natural causes and had sustained the abrasions on his face by falling. The eyeglasses of the deceased were found near the body; one lens was missing, the right one was still in place and was perforated and blood-stained. The homi-

cidal nature of the case was then apparent. At necropsy, the bullet which had perforated the spectacle lens and then passed between the eyelids and through the eyeball, was found in the brain. Photographs of the deceased without and with the eyeglasses in place are seen in figure 2. The photograph in figure 3 is that of a deceased person shot through the inner canthus of the left eye. The wound is completely concealed by the closed eyelids.

FIG. 1. Small fatal homicidal ice pick stab wound of frontal portion of scalp (arrow). Wound concealed by hair which has been cut away. Weapon penetrated skull and deeply into brain.

DISPOSAL OF BODIES BY DISMEMBERMENT AND BURNING

The mutilation and dismemberment of a murdered body may destroy all possibility of identification and determination of the cause of death. In many cases, however, the cause of death can be determined despite extensive mutilation of the murdered body by dismemberment, burning or by chemical agents.

In one case the head and all four dismembered extremities of a murdered

FIG. 2. *Left*—Homicidal bullet wound through right eyeball concealed by closed eyelids. *Right*—Photograph with eyeglasses in place to show bullet perforation in right lens. When body was first found bullet wound was not recognized. Eyeglasses of deceased found near body. Bullet recovered in brain.

body were recovered. Two blunt weapon wounds were visible on the top and back of the head and there were blunt weapon defense wounds on the right hand. The four extremities were found tightly packed in a wooden box in the entrance way to a store; the head rolled out of the back of a garbage truck making collections of refuse in the same neighborhood. Subsequently the hips and thighs were found but not the upper part of the torso. The skull was fractured and the brain lacerated. The larynx was also fractured.

Bodies found burned in conflagrations should always be examined with the possibility that the deceased had been murdered and then incinerated to destroy evidence of the crime. It is wise to examine the blood chemically

FIG. 3. Homicidal bullet wound through inner canthus of left eye concealed by closed eyelids. Bullet recovered in brain.

for the presence of carbon monoxide, the absence of which would indicate that the deceased was dead before the body was burned. There are several homicide cases recorded in the files of the Office of the Chief Medical Examiner of New York City in which charred bodies of persons at first thought to have been accidentally burned to death in conflagrations, were found at necropsy to have died of depressed fractures of the skull.

In a case investigated by Dr. Thomas A. Gonzales, Chief Medical Examiner of New York City, the charred dismembered head and torso and the charred segments of the lower limbs of the body of a negro were found among the embers of a bonfire in a vacant lot. Despite extensive incineration of the tissues, a comminuted depressed fracture was found in the occipital portion of the skull. That the deceased was dead when placed in the fire was corroborated by the absence of carbon monoxide from the blood. The perpetrator was apprehended and confessed that he had bludgeoned the victim to death, dismembered the body and tried to dispose of it by incineration in the bonfire.

Submerged Bodies

In homicidal cases in which the body has been submerged for a variable length of time, in addition to the anatomical evidences of drowning and wounding, a chemical test for chlorides should be carried out on samples of blood removed from the right and left sides of the heart according to the method devised by Gettler.[11] The inhalation of salt water into the lungs is indicated by a higher concentration of chloride in the blood from the left side; the inhalation of fresh water produces a lower concentration of chloride on the left side. The test is vitiated by a patent foramen ovale and cannot be carried out in decomposed bodies in which the putrefactive gases have forced the blood out of the heart.

Penetrating stab wounds and bullet wounds and non-penetrating blunt force injuries are occasionally found in bodies recovered after varying periods of submersion. Suicidal injuries such as incised wounds of the throat and wrists are not infrequently encountered. Submerged bodies, especially those recovered from rivers and harbors in which there is a heavy shipping traffic, frequently show postmortem injuries which may be confusing even to the experienced observer.

An example of such postmortem injuries is illustrated by the case of a decomposed torso found floating in the Hudson River. Two days later, the right lower extremity with the distal half of the leg missing was found in the East River about five miles away. The next day, the corresponding left lower extremity was found floating in the Hudson River about two miles away. The torso and the extremities were obviously parts of the same body. By means of the cleaning and laundry marks in the clothing found on the left extremity, the body was identified as that of a 60-year old white man who one week before committed suicide by jumping off the back of a

ferry boat into the Hudson River. Prior to jumping he swallowed the contents of a bottle of poison which he purchased in a drug store earlier the same day. The body was probably dismembered by the propeller blades of the ferry boat. The identification definitely established the suicidal character of the death and the fact that the dismemberment occurred postmortem after submersion.

Procedure in Poisoning Cases

In cases in which there is a definite indication or suspicion of poisoning, the organs such as the brain, liver, kidneys, stomach and its contents, lungs and bones, and the blood and urine, should be saved for chemical examination. These should be carefully weighed and measured, placed in clean labelled containers without contamination, and promptly delivered and properly identified as to source, to the toxicologist. The careful examination of the organs for evidences of disease or traumatic injury should not be neglected, and pieces of tissue should be saved for microscopic examination. Many poisons produce characteristic histologic alterations, and certain disease processes, not visible grossly, which clinically simulate the action of poison, may become apparent.

Where the necropsy findings definitely point to a certain poison or group of poisons, the toxicologist should be so informed in order that he may directly test for the suspected substance. In the absence of such leading information, considerable time may elapse before the routine systematic analysis for all poisons will reveal the substance present. This delay may hamper the investigation of the case by the police authorities.

Details of Necropsy Requiring Special Consideration

The necropsy in a homicidal case involves much more than the mere determination of the cause of death. A considerable amount of information must be obtained in anticipation of questions which may subsequently arise in connection with it.

Shooting Cases

The description of bullet wounds should include those details which help to indicate the distance from the body, of the weapon used in firing the shot. A contact bullet wound is produced when the gun is fired with its muzzle held against the skin and its appearance is fairly characteristic. The skin surrounding the perforation does not contain any embedded powder grains because the full effect of the discharge is blown into the track of the wound, which may be blackened and burned for a variable distance. The perforation in the skin varies in size and is often large and irregularly lacerated. However, it is sometimes small and regular in appearance. In some contact wounds, a distinctive abraded impression of the muzzle of the weapon is found on the skin.

The two photographs in figure 4 illustrate two different patterned impressions of the muzzle of a pistol on the skin in contact bullet wounds. In the picture on the left, the right temple reveals the clear cut impression of the muzzle of a 32-caliber Colt automatic pistol used by the deceased to commit suicide. In the picture on the right, there are three homicidal bullet wounds, one a closeup and two contact wounds. The contact wound on the cheek has an inverted keyhole pattern, the pyramidal shape of the abrasion (arrow) corresponding to the outline of the end of the rib found on top of the barrel of certain revolvers like the Iver-Johnson.

A close-up wound is produced when the weapon is fired at close range and characteristically reveals the effects on the skin of the powder grains and

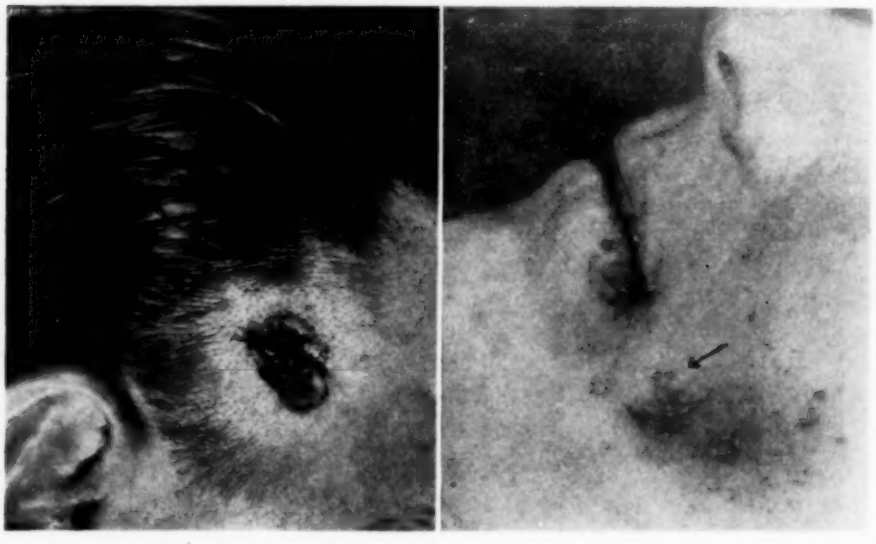


FIG. 4. *Left*—Patterned impression of muzzle of 32-caliber Colt automatic pistol on right temple. Suicidal contact bullet wound. *Right*—Patterned impression of end of rib on muzzle of revolver. Homicidal contact bullet wound.

flame of the discharge in addition to the bullet perforation. The distribution and appearance of the embedded powder grains, the extent of the burn and smoke deposit, and their relation to the bullet perforation should be carefully noted.

In a distant shot, the muzzle of the gun is held beyond the reach of the flame and powder grains of the discharge; the surface wound consists only of the bullet perforation and varies in appearance according to the angle at which the bullet strikes.

A valid opinion as to the distance from which a shot was fired to cause a wound on a clothed part of the body can only be given after an examination of the clothing. The powder grains, flame and smoke of the discharge

in a close-up shot are deposited on the clothes and only the bullet may reach the skin, as in a distant shot.

Preservation of Bullets and Other Objects Recovered at Necropsy

All bullets and bullet fragments, shotgun pellets and slugs must be recovered from the body. In contact wounds inflicted with a shotgun, the felt wads of the cartridge may also be found. The bullets removed at the necropsy are an important part of the corpus delicti, and by their composition, caliber and rifling marks may be traced to one or more weapons used

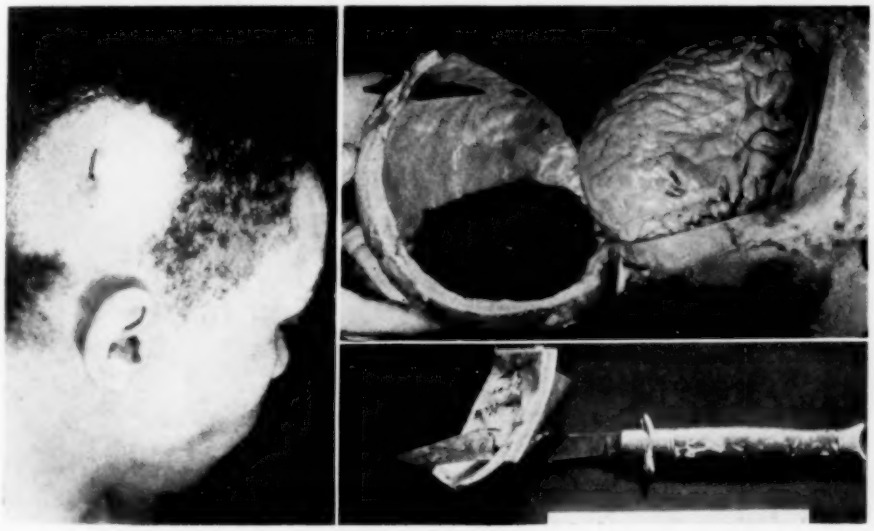


Fig. 5. *Left*—Penetrating stab wound in right parietal portion of scalp. Note slight bulge produced by projecting end of underlying knife blade. *Upper Right*—Top of skull removed and laid back to show length of broken-off knife blade which penetrated skull and brain. Note stab wound in dura; large subdural hemorrhage flowed out and was collected in hollow of skull at time of autopsy. *Lower Right*—Broken-off blade embedded in block of bone removed at autopsy and offered as evidence at trial. Handle of knife with broken blade stump found on perpetrator, included in photo to show matching broken ends of blade. After being stabbed deceased chased his assailant for distance of a block.

in the commission of the crime. Occasionally, bullets of different caliber are recovered from the same body, indicating that more than one weapon was used in the shooting.

The bullets removed from the body must be carefully described and marked by the medical examiner for purposes of identification. Care must be taken during the removal and marking of a bullet not to mar any of the distinctive rifling marks on the sides of the missile because these marks are used for purposes of comparison with test bullets fired from the pistol believed to have been used in the crime. The bullets should be safely stored

in a locked container until they are delivered for testing to a member of the Ballistics Bureau of the Police Department, who will furnish a receipt for them; upon their return from the ballistics department, the medical examiner will give a receipt acknowledging the fact. These precautions are necessary in order that the bullets may be introduced properly by the medical examiner as evidence at any subsequent criminal proceeding.

Similarly, in stabbing cases, the broken-off fragment of any weapon, such as a knife blade, ice pick or scissors blade, found in the body should be carefully preserved as evidence and for future comparison with a weapon from which it may have been derived.

FIG. 6. *Left*—Small penetrating stab wound in forehead. *Right*—Calvarium and brain removed showing broken off closed scissors blades stuck in right frontal bone projecting into cranial cavity. The blades pierced the frontal lobe of the brain resulting in a delayed fatal hemorrhage.

If a broken-off knife blade is found embedded in bone which it has perforated, a block of the bone containing the blade can be removed with a saw or chisel and preserved as an exhibit which can be offered later in evidence to show the weapon and the extent of its penetration. An example of such a case is illustrated by the photographs in figure 5. The picture on the left shows a stab wound in the scalp beneath which a broken-off knife blade was found perforating the skull and underlying brain. In the top picture on the right, the skull cap has been removed and turned back to show the length and point of the blade which pierced the meninges and the brain. A large subdural hemorrhage was allowed to escape into the hollow of the skull before the photograph was taken. The perforation in the dura is readily seen. In the bottom picture, the broken blade in its undisturbed position in the bone is shown removed from the skull and placed next to the pocket knife

used by the perpetrator. The broken-off blade in the bone was admitted as evidence in the trial. In this case, the deceased, a 17-year old boy, after being stabbed in the head, ran a block after his assailant and attempted to strike him before collapsing. Death occurred rapidly because of the large subdural hemorrhage from the cut vessels on the surface of the brain. There was no bleeding along the track of the wound in the brain tissue.

In other cases of stab wounds of the brain the injured brain tissue may bleed slightly at first and the victim remain conscious for a variable period of time during which the nature and seriousness of his injury are not recognized. The entrance wound may be small. The sudden onset of secondary bleeding in the injured brain tissue causes rapid unconsciousness and death. In a case of this type, illustrated in figure 6, the victim was stabbed through the forehead with a closed scissors; the small entrance wound can be seen in the photograph on the left. He remained conscious and walked into the accident room of a hospital where he suddenly became unconscious and died two days later. In the photograph on the right, the broken-off scissors blades can be seen perforating the right frontal bone. There was a large hemorrhage into the frontal lobe of the brain which was pierced by the weapon.

Occasionally, a broken-off piece of a blunt instrument is found in a penetrating wound. Metallic fragments such as radiator ornaments, door handles and button fasteners, and glass fragments may be found in the body of a person fatally injured by an automobile. Such objects are important for purposes of comparison with the suspected damaged vehicle in "hit-and-run" automobile cases and should always be saved.

Examination of Spine

If there is any indication that the spine or spinal cord may have been injured in the track of a bullet or stab wound, such injuries must be definitely established by the necropsy. Aside from the relation of a spinal cord injury to the cause of death, the finding of such an injury may have considerable significance should the question subsequently arise as to whether or not the deceased could have walked after having received his wounds.

Sexual Assaults

In homicidal cases, in which there is suspicion or evidence that a sexual assault, such as rape or sodomy, was commited on the deceased, the necropsy must include a careful examination of the genitalia and anal region to determine the presence of injury. Fresh and stained smears of secretions taken from the vagina and anal region and of any seminal deposits and stains on the pubic hairs and skin surrounding the vulva and suspicious stains on the undergarments should be examined for spermatozoa.[12] Ultraviolet light is helpful in rendering seminal stains on certain types of cloth more visible.

If many suspicious stains are found, the Florence test may first be carried out and only those stains reacting positively need be examined further for spermatozoa.

An attempt should be made to determine the group specificity of the seminal stains. The latter procedure should be carried out by a competent serologist. The organs of the deceased, especially the brain, should be examined chemically for the presence of poisons which might have been administered to the deceased to overcome resistance during the commission of the crime, and which might have caused the death.

Examination of Stomach Contents

In homicidal cases, the contents and the degree of digestion of any food in the stomach and intestines should be carefully noted. The presence of certain recognizable particles of food and the degree of digestion may suggest whether or not the deceased had recently eaten and in connection with other information may help in the determination of the postmortem interval and also in the identification of the deceased. The length of time that food remains in the stomach before passing into the intestine varies considerably and any opinion based on the necropsy stating the time before death that food was eaten should be guarded. In injured and comatose persons ingested food may remain in the stomach for days.

Toxicological Examinations

A quantitative chemical examination of the brain to determine the presence of ethyl and methyl alcohol should be carried out routinely in all cases of homicide in which the deceased has been found dead or has survived for less than 24 hours in the hospital after having received his injuries. If the survival period is longer than 24 hours, any ethyl alcohol present in the tissues will have disappeared by oxidation although methyl alcohol may persist for a longer time. The presence of alcohol in the brain indicates that the deceased had consumed it during the 24-hour period prior to death.

The amounts of alcohol recovered quantitatively in the brain are expressed by Gettler and Tiber,[13] in terms of plus amounts and are designated as: a trace, 1 +, 2 +, 3 + and 4 +. These designations correspond to amounts of alcohol as follows:

trace	0.005 to 0.02 per cent.
1 +	0.03 to 0.10 per cent.
2 +	0.11 to 0.25 per cent.
3 +	0.26 to 0.40 per cent.
4 +	0.41 to 0.60 per cent.

Amounts of alcohol above 0.25 per cent are considered indicative of "intoxication." The amount of alcohol recovered from the brain does not necessarily indicate the amount consumed. Persons addicted to alcohol are able to oxidize it more rapidly than those who are not and, therefore, may

consume more and have less residual alcohol in the brain after a certain period of time. In estimating the probable state of intoxication from the amount of alcohol recovered from the brain, the period of time that the deceased has survived since the last ingestion of alcohol must be considered. The amount of alcohol recovered at necropsy is not significantly altered by the postmortem interval.

Chemical examination for other poisons should be made in certain types of cases. Depressant poisons such as chloral, barbiturate compounds, morphine and hyoscine, chloroform and other anesthetic compounds, should be tested for in homicidal cases associated with robbery, sexual assault and criminal abortion where the deceased is found dead in the home or in a doctor's or midwife's office. In such cases, a routine systematic analysis for all poisons should be carried out on the organs.

Examination of Finger Nail Scrapings and Hair

The scrapings from under the finger nails and from the hands of the deceased should be carefully examined for minute fragments of skin, strands of hair and cloth fibers which the deceased may have removed from the assailant during a struggle. This procedure should be carried out in cases of homicidal strangulation, smothering and choking and in deaths from homicidal assault with blunt or sharp weapons.

It is useful to remove small tufts of hair from the scalp and other parts of the body of the deceased and to save them for future comparison with hairs found on subsequently confiscated weapons. Hairs from the deceased should be saved in homicidal cases where death has been caused by injuries of the head inflicted with blunt weapons and also in cases of death by "hit-and-run" automobiles in which some of the deceased's hairs may have been torn out and remained attached to various parts of the vehicle such as the bumper, fender or headlight. Vance [14] has described the technic and pointed out the medicolegal applications of hair examinations.

Routine Blood Grouping of Deceased

The blood group of the deceased should be determined in all cases of homicide. This information may prove very significant, in the event that a blood stain found on the clothing of a suspect is of the same group as the blood of the deceased and different from the suspect's own blood group; in such a case, there would be strong presumption as to the origin of the stain.

Blood stains on the clothing, suspected of belonging to the assailant and not to the deceased, should be grouped if possible, and the group compared with that of the deceased's blood and also with that of the suspect.

Wiener [15] has shown that by utilizing the four major blood groups O, A, B and AB of Landsteiner, the subgroups of A and AB discovered by von Dungern and Hirszfeld in 1910, the three blood types M, N and MN, and

type P, determined by the factors M and N, and P which were discovered by Landsteiner and Levine in 1928 and which are independent of the major groups, and the eight Rh blood types which have been evolved from the recent discovery of the Rh factor by Landsteiner and Wiener in 1937, it is now possible to distinguish 288 different kinds of human blood instead of the original four groups. The major blood groups and subgroups in all furnish six groups, O, A_1, A_2, B, A_1B, A_2B; there are the three independent blood types M, N, MN and two types determined by the presence or absence of factor P; the eight Rh blood types which are independent of the major groups and subgroups and of the types M, N, MN and of P, have been designated by Wiener as Rh_0, Rh_1, Rh_2, Rh_1Rh_2, Rh-, Rh′, Rh″, Rh′Rh″. By multiplying together the number of subdivisions in each of the above four categories, namely $6 \times 3 \times 2 \times 8$, the product of 288 different combinations or kinds of human blood is obtained.

The following homicide case [16] recently investigated by the Office of Chief Medical Examiner, the Police Department and the District Attorney's Office of New York County (Borough of Manhattan) is an excellent example of the value of group determinations in scientific crime detection.

At 2 o'clock in the morning, in the dim-out, a watchman of a building saw the figure of a man dragging a large object down the steps of an adjacent tenement house stoop and deposit it on the sidewalk a short distance away. The man then walked away. The watchman investigated the object and found it to be the body of a dead woman. While waiting for a police officer to arrive he observed the man who had carried the body return to the house and a few minutes later he saw him coming out again. The suspect was arrested but when confronted with the body stated that he had never seen it before. At the time of his arrest, he was carrying an almost empty wine bottle wrapped in newspaper under his arm; he admitted purchasing the bottle of wine in a neighborhood liquor store.

The examination of the body and subsequent necropsy by Dr. Morgan Vance, Deputy Chief Medical Examiner, revealed that death had resulted from strangulation. There were abrasions and a ligature mark on the neck. The distribution of the postmortem lividities indicated that the body had been moved after death and the disappearance of rigor mortis indicated that it had been dead for some time. A large amount of alcohol was found in the brain.

When the body was found the left shoe and stocking and the hat of the deceased were missing. Near the head there was a rolled up brown paper bag which contained the missing stocking. Several blocks away a package was found in a refuse can; it contained two men's shirts, a woman's hat and a left shoe similar to the right shoe of the deceased, and two men's handkerchiefs knotted together with several wisps of hair entangled in the knots. In the suspect's room a shiny dry stain was found near the bed on the oilcloth floor covering and a blood stain on the bed sheet. At the request of the

District Attorney investigating the case, the suspect consented to have his blood typed. The oilcloth covered with the shiny stain, the blood-stained bed sheet and the shirts and handkerchiefs found with the deceased's hat and shoe were sent to the serological laboratory of the Medical Examiner's Office for examination.

The following results were obtained by Dr. Alexander S. Wiener, Serologist of the Medical Examiner's Office. The deceased's blood was group A and tests on her tissues proved her to be a secretor of group A substance. The suspect was group B. The blood stain on the bed sheet by chemical and precipitin tests was proved to be human blood but there was not enough material for a group determination. The dry stain on the floor was found to contain albumin, nasal epithelial cells and also group A substance, the group being similar to that of the deceased. The shirts and handkerchiefs found in the package with the deceased's hat and shoe, contained group B substance which had been secreted in the sweat and nasal discharge of the person who had used them. The group substance in the shirts and handkerchiefs was therefore the same as that of the suspect. The hairs found in the knotted handkerchiefs were similar to those on the deceased's head. The brown paper bag containing the stocking, found near the head of the deceased, was traced to the liquor store where the suspect admitted he had bought the bottle of wine he was carrying when arrested. The wine had been wrapped in such a bag when it was sold.

The suspect at first denied any connection with the crime and was held as a material witness. When the significance of the incriminating scientific circumstantial evidence was explained to him, he confessed the murder, stating that he had manually strangled the deceased on the bed in his room, about twenty-four hours before removing her body to the sidewalk. He claimed that he strangled the victim because she had become drunk and noisy and had refused to leave his room after drinking most of his wine. After the murder he had placed the body face down on the floor during which time the secretion from the nose and mouth drained out on the oil cloth to produce the stain which contained the group A substance. He had used his soiled handkerchiefs as a ligature to keep the deceased's mouth closed. After having carried the deceased's body from his room, he had gone back and wrapped the soiled handkerchiefs and his shirts and the deceased's hat and left shoe in the package which he discarded in a refuse can several blocks away. When he returned again to the room, he found that he had overlooked a stocking and put it in the brown paper bag. He had this bag containing the stocking in his pocket when he was arrested but managed to drop it unnoticed near the head of the victim when he was asked to view the body.

Examination of Clothing as Part of Corpus Delicti

The clothing of the deceased in a homicide case is an important part of the corpus delicti and must be carefully described and marked for identifica-

tion by the medical examiner. Blood stains, and cuts and perforations produced by weapons and missiles are noted, as well as their location in relation to the wounds on the body. The examination of the clothing, as already pointed out, is most important in shooting cases, enabling the examiner to determine whether a certain wound on a covered portion of the body resulted from a close-up or distant shot. The clothes are also helpful in determining the direction of a bullet track, in cases where the bullet has passed completely through the body, producing entrance and exit wounds which are not readily differentiated. In such cases, the bullet may pass out of the skin through the exit wound but not completely through the clothing, which circumstance will indicate the direction of the bullet.

In a recent murder trial in New Jersey [17] presided over by Judge Egbert Rosecrans, the defendant admitted the fatal shooting but claimed that he did it in self-defense and there seemed to be strong corroborative evidence that this was so. The fatal bullet had passed completely through the body. The victim was operated upon and during this procedure a bullet wound on the front of the abdomen was obliterated. A bullet perforation on the back was interpreted as an entrance wound by the physician who performed the necropsy. Because of this interpretation, the self-defense plea of the perpetrator was not believed and he was indicted and tried for the murder.

Upon inquiry it was learned that the clothing worn by the deceased when he was shot, had not been examined. Fortunately it had been saved and was examined during the trial. The fatal bullet had perforated all the garments in front but not in the back, indicating clearly that the bullet entered through the front of the body, a fact consistent with the claim of self-defense. The defendant was acquitted.

Other Examinations Connected with Necropsy

A careful examination should also be made of any ligatures, gags or wads that may be found around the neck or mouth, or in the mouth and throat of the deceased, in cases of homicidal strangulation by ligature, and choking. Ropes, wires or any improvised ligature found on the extremities or body of a deceased person are described and saved.

Preservation of Evidential Material

The clothing of the deceased and other evidential material, such as ligatures and gags, are carefully preserved and delivered by the identifying police officer to the prosecuting attorney for use in any subsequent criminal prosecution of the case. The clothing of the deceased person must not be returned to the family. In those cases where the deceased dies in the hospital some time after he has received his injuries, the hospital authorities must be instructed not to deliver the clothing of the deceased to members of the family, but to save it for subsequent examination by the medical examiner at the time of the necropsy.

Postmortem Findings and Conclusions Reported to Police and Prosecuting Attorney

Upon the completion of the investigation and necropsy by the medical examiner in a case of homicidal death, the police authorities should be notified promptly of the findings in order to help them in their investigation of the crime. It is important to report cases of unsuspected violent death discovered at necropsy which are definitely or possibly homicidal. If the necropsy in an apparently suspicious case already under investigation by the police, does not reveal any evidence of criminal violence the police should also be informed of the findings.

The medical examiner's report is carefully corrected and a copy delivered to the prosecuting attorney. It is not permissible to divulge the findings in a homicidal case to any one else. Permission to inspect the postmortem records may be granted only by the district attorney.

In those cases which subsequently come to trial, the medical examiner is an important witness for the prosecution. However, he must always remember that he is not a prosecuting witness and must not be biased. His opinions should always be warranted by the findings in his investigation and necropsy. He should consider himself *amicus curiae*.

Summary

Inadequacies in the statutes pertaining to the Office of Coroner and Medical Examiner and in the organization and function of these medicolegal agencies are responsible for unsatisfactory postmortem investigation of homicide in most jurisdictions in the United States.

A fundamental defect in the statutes is the failure to recognize and provide for the fact that in many violent deaths there are not any externally obvious or suspicious signs of violence on the body of the deceased.

It is only by the routine investigation from the very beginning, of all sudden and unusual as well as suspicious and violent deaths, that unsuspected homicides will be detected. Paradoxically, those medicolegal systems which are concerned only with criminal deaths or obviously suspicious and violent ones fail most often to detect unlabelled homicides.

The medical examiner's system in New York City, Essex County (New Jersey), Nassau County (New York), and the State of Maryland, which was established in these places by almost identical statutes, possesses certain desirable features. It provides for the investigation of all violent, sudden, suspicious and unusual deaths and deaths which have occurred without benefit of medical attention. It functions independently of other government agencies insofar as the medical investigations are concerned and it places upon the medical examiner alone the responsibility and the authority for the necessity and the performance of the necropsy in any medical examiner's case. Every stage of the medical examiner's investigation is carried out by trained specialists in legal medicine.

The postmortem examination in a case of homicide properly commences with the investigation by the medical examiner, or other authorized and qualified medical person, of the dead body at the scene where it is found. A complete and careful necropsy is subsequently performed on the body of the deceased by the medical examiner to determine the cause of death. The necropsy should include certain routine and special examinations, not necessarily connected with the cause of death, but which may subsequently prove important in the development of the case.

BIBLIOGRAPHY

1. HELPERN, M.: Postmortem examination in homicides, Am. Jr. Med. Jurisp., 1938, i, 165.
2. WEINMANN, G. H.: Compendium of the Statute Law of Coroners and Medical Examiners in the United States, National Research Counc. Bull. No. 83, Washington, 1931.
3. Laws of New York 1915, ch. 284.
4. New York City Charter 1901, sections 1570 and 1571, as added by L. 1915, ch. 284, section 2, relate to the Office of Chief Medical Examiner:

"Section 1570: Organization of Office, Officers and Employees.—There shall be established the Office of the Chief Medical Examiner of the City of New York. The head of the Office shall be called 'Chief Medical Examiner.' He shall be appointed by the Mayor from the Classified Service and be a doctor of medicine, and a skilled pathologist and microscopist.

"The Mayor may remove such officer upon stating in writing his reasons therefor, to be filed in the office of the Municipal Civil Service Commission and served upon such officer, and allowing him an opportunity of making a public explanation. The Chief Medical Examiner may appoint and remove such deputies, assistant medical examiners, scientific experts, officers and employees as may be provided for pursuant to law. Such deputy medical examiners and assistant medical examiners, as may be appointed, shall possess qualifications similar to those required in the appointment of the Chief Medical Examiner. The office shall be kept open every day in the year, including Sundays and holidays, with a clerk in constant attendance at all times during the day and night."

"Section 1571: Violent and Suspicious Deaths; Procedure.—When, in the City of New York, any person shall die from criminal violence, or by a casualty, or by suicide, or suddenly when in apparent health, or when unattended by a physician, or in prison, or in any suspicious or unusual manner, the officer in charge of the station house in the police precinct in which such person died shall immediately notify the Office of the Chief Medical Examiner of the known facts concerning the time, place, manner and circumstances of such death. Immediately upon receipt of such notification the chief medical examiner, or a deputy or assistant medical examiner, shall go to the dead body and take charge of the same. Such examiner shall fully investigate the essential facts concerning the circumstances of the death, taking the names and addresses of as many witnesses thereto as it may be practicable to obtain and, before leaving the premises, shall reduce all such facts to writing and file the same in his office. The police officer so detailed shall, in the absence of the next of kin of deceased person, take possession of all property of value found on such person, make an exact inventory thereof in his report, and deliver such property to the police department, which shall surrender the same to the person entitled to its custody or possession. Such examiner shall take possession of any portable objects which, in his opinion, may be useful in establishing the cause of death, and deliver them to the police department."

"Section 1571 a: Autopsies; Findings.—If the cause of such death shall be established beyond a reasonable doubt, the medical examiner in charge shall so report to his office. If, however, in the opinion of such medical examiner an autopsy is necessary, the same shall be performed by a medical examiner. A detailed description of the findings written during the progress of such autopsy and the conclusions drawn therefrom shall thereupon be filed in his office."

"Section 1571 b: Report of Deaths, Removal of Bodies.—It shall be the duty of any citizen who may become aware of the death of any such person to report such death forthwith to the Office of the Chief Medical Examiner and to a police officer, who shall forthwith notify the officer in charge of the station house in the police precinct in which such person died. Any person who shall wilfully neglect or refuse to report such death or who, without written order from the medical examiner shall wilfully touch, remove, or disturb the body of any such person, or wilfully touch, remove, or disturb the clothing, or any article upon or near such body, shall be guilty of a misdemeanor."

"Section 1571 c: Records.—It shall be the duty of the Office of the Chief Medical Examiner to keep full and complete records. Such records shall be kept in the office, properly indexed, stating the name, if known, of every such person, the place where the body was found and the date of death. To the record of each case shall be attached the original report of the medical examiner and the detailed findings of the autopsy, if any. The office shall promptly deliver to the appropriate district attorney copies of all records relating to every death as to which there is, in the judgment of the medical examiner in charge, any indication of criminality. All other records shall be open to public inspection as provided in section fifteen hundred and forty-five. The appropriate district attorney and the police commissioner of the city may require from such office such further records, and such daily information, as they may deem necessary."

"Section 1571 d: Oaths and Affidavits.—The Chief Medical Examiner, and all deputy or assistant medical examiners, may administer oaths and take affidavits, proofs and examination as to any matter within the jurisdiction of the office."

See also revised New York City Charter 1938, ch. 39, sections 874 to 879.

L. New Jersey 1927, ch. 106 and L. New York 1936, ch. 879 pertain to the Office of Chief Medical Examiner in Essex County and Nassau County, respectively; also L. Maryland 1939, ch. 369.

5. Annual Statistical Reports of the Chief Medical Examiner of the City of New York.
6. Photographs of the undisturbed dead body at the scene in the first two of the following examples were reproduced in Helpern, M. *op. cit. supra*, no. 1, p. 167.
7. For the photograph of the undisturbed dead body at the scene in this case, see Gonzales, T. A., Vance, M., and Helpern, M.: Legal medicine and toxicology, 1940, D. Appleton-Century Co., New York, p. 277.
8. For a more detailed description and discussion of the signs of death, see *id.* p. 49 to 65.

   Glaister, J.: Medical jurisprudence and toxicology, ed. 7, 1942, Williams and Wilkins Co., Baltimore.

   Herzog, A. W.: Medical jurisprudence, 1931, The Bobbs-Merrill Co., Indianapolis.

   Smith, Sydney: Forensic Medicine, ed. 4, 1934, J. & A. Churchill, Ltd., London.

   Smith, Sydney and Cook, W. G. H.: Taylor's principles and practice of medical jurisprudence, ed. 9, 1934, J. & A. Churchill, Ltd., London, vol. 1, p. 195 to 263.

   Strassmann, George: F. Strassmanns Lehrbuch der Gerichtlichen Medizin, ed. 2, Stuttgart, Ferdinand Enke, 1931.
9. For a discussion of trauma and its complications, and for examples of medical examiners' findings in homicidal, suicidal and accidental deaths, the reader is referred to Gonzales, T. A., Vance, M., and Helpern, M., *op. cit. supra.*, no. 7, p. 88 to 370.

MARTLAND, H. S.: Medical examiners' findings in deaths from shooting, stabbing, cutting and asphyxia, Symposium on The Medicolegal Necropsy, 1934, The Williams and Wilkins Co., Baltimore, p. 66 to 160.

MORITZ, A. R.: The pathology of trauma, 1942, Lea & Febiger, Philadelphia.

SMITH, SYDNEY, *op. cit. supra.*, no. 8.

GETTLER, A. O.: Toxicology in the medicolegal necropsy, Symposium on The Medicolegal Necropsy, 1934, The Williams and Wilkins Co., Baltimore, p. 50 to 66.

10. HELPERN, M.: Unusual fatal stab wounds of head and neck, Am. Jr. Surg., 1934, xxvi, 53.
11. GETTLER, A. O.: A method for the determination of death by drowning, Jr. Am. Med. Assoc., 1921, lxxvii, 1650.
12. GONZALES, T. A., VANCE, M., and HELPERN, M.: *op. cit. supra.*, no. 7, p. 359 to 370.

POLLAK, O. J.: Semen and seminal stains, Arch. Path., 1943, xxxv, 140–196.

13. GETTLER, A. O., and TIBER, A.: Quantitative determination of ethyl alcohol in human tissues, Arch. Path., 1927, iii, 75; Alcoholic content of the human brain, Arch Path., 1927, iii, 218.
14. VANCE, B. M.: The medicolegal examination of hairs, New England Jr. Med., 1938, ccxviii, 22, 914–918.
15. WIENER, A. S.: Blood groups and blood transfusion, ed. 3, 1943, Charles C. Thomas, Springfield, Ill.

WIENER, A. S.: The Rh blood types and some of their applications, Am. Jr. Clin. Path., 1945, xv, 106.

WIENER, A. S.: Rh factors in clinical medicine, Jr. Lab. and Clin. Med., 1945, xxx, 957.

16. Assistant District Attorney Louis A. Pagnucco of the New York County District Attorney's office supervised the investigation of this case and I am indebted to him for the interesting details.
17. State of New Jersey vs. Frank Pulsinelli, Warren County Court of Oyer and Terminer, December Term, 1940.

CASE REPORTS

EXCESSIVE SELF-ADMINISTERED DOSAGES OF THYROID EXTRACT *

By DAVID GOLDFINGER, M.D., *Chicago, Illinois*

THERE are numerous reports in the literature regarding the effects of thyroid feeding in animals. There are only a few reports dealing with the effect of large doses of thyroid in man. The following case report is of interest because of the huge doses of thyroid extract consumed over a period of one year, by an individual subsequently proved unstable, for the concealed purpose of self-destruction.

CASE REPORT

On December 4, 1941, a white, married, 28 year old woman presented herself for weight reduction. The past history revealed the usual childhood diseases, a tonsillectomy at age 5, but no serious illness. At age 24 (1937) a Caesarean section was performed for placenta previa. The patient admitted previous medical care for weight reduction without results.

The physical examination revealed a well developed and overly nourished woman 5'3" (60.2 cm.), weighing 166½ lbs. (75.6 kg.). The head and neck were negative. The thyroid was not palpable. The lungs were clear. The heart was essentially negative. The blood pressure was 140 mm. Hg systolic and 80 mm. diastolic and the pulse rate was 72. The abdomen was protuberant with a healed hypoumbilical surgical scar. The extremities and the reflexes were negative. The pelvic and rectal examinations were negative. The preliminary laboratory survey showed a negative urinalysis and negative blood count. The Kahn test was negative. The basal metabolic rate was plus 1 per cent. Fluoroscopy of the chest was negative.

The usual method of weight reduction by dietary restriction was explained to the patient, but she rejected this plan, asserting that simple dietary restriction had proved valueless in the past. She was given thyroid extract (U.S.P.XI) in daily doses of four grains with the usual dietary instructions. Weight reduction was slow, and on January 21, 1942, the dosage was increased to six grains, since there were no subjective complaints or cardiovascular effects. On May 7, 1942, the weight was 132½ lbs. (60.2 kg.), the blood pressure was 142 mm. Hg systolic and 72 mm. diastolic, and the pulse rate was 90. The administration of thyroid was stopped. The patient returned on June 2, 1942, weighing 136¾ lbs. (62.1 kg.), the blood pressure was 132 mm. Hg systolic and 74 mm. diastolic, and the pulse rate was 74. Thyroid (6 grains daily) was reinstituted. In two weeks she lost 7 lbs. (3.1 kg.), and the blood pressure and pulse rate again increased. The thyroid dosage was reduced and, because of nervousness, was stopped two days later. However, the nervousness and weight loss continued, and it was discovered that the patient's lack of response to sedation was because she had been surreptitiously taking 20 to 25 grains of thyroid daily throughout the summer. The patient had been despondent. In November, 1942, the weight was 103 lbs. (46.8 kg.), the blood

* Received for publication April 5, 1945.
From the Department of Medicine, Chicago Medical School.

pressure 120 mm. Hg systolic and 80 mm. diastolic, and the pulse rate 160. She was hospitalized, during which time it was discovered that she had taken approximately 100 grains daily for an unknown period. The basal metabolic rate was plus 34 per cent. The electrocardiogram showed (figure 1, A) a rate of 105, some slurring of the QRS complexes, and flattening of the T-waves. The patient received no thyroid after hospitalization but she refused to eat, and continued to lose weight,

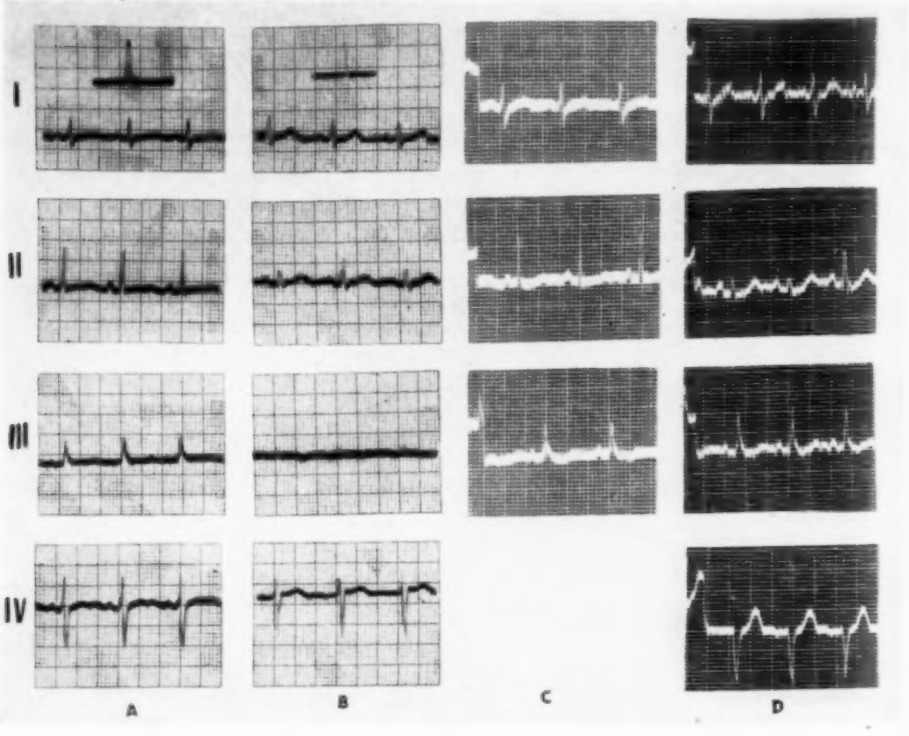


FIG. 1.

A. The electrocardiogram taken November 27, 1942 shows the standard leads and CF IV. The patient had consumed 100 grains of desiccated thyroid daily for an unknown period prior to this.

B. Electrocardiogram taken April 18, 1943, showing a lower standardization than A, slightly slower rate and T-waves of higher amplitude. No thyroid had been taken in four months.

C. Electrocardiogram taken March 30, 1944, showing the effects of digitalization; no thyroid had been ingested for six months.

D. Electrocardiogram taken January 20, 1945, nine days before sudden death. Thyroid and digitalis had not been administered.

finally reaching 80 lbs. (36.3 kg). She was sent to a mental hospital for psychiatric care.

The patient improved and gained weight. In April, 1943, she was allowed to go on walks alone. The electrocardiogram showed (figure 1, B) a rate of 97, and the T-waves in Leads I and II were definitely of much higher amplitude than in figure 1, A, and if the substandardization of this tracing be taken into account, comparatively, the T-waves in this tracing were much higher. Suddenly, the heart

rate and her nervousness increased, and it was discovered that she had purchased huge quantities of thyroid while unobserved, and had consumed doses conservatively estimated at 100 grains daily. Several thousand two-grain thyroid tablets were found hidden in the patient's room, as were also 15 empty bottles each of which had contained 100 two-grain tablets.

As far as is known, this thyroid feeding was discontinued in September 1943. After this the weight stabilized at 115 lbs. (52.2 kg). The tachycardia persisted, and on two occasions was slowed by digitalization, but the patient stopped this medication voluntarily because of nausea. An electrocardiogram, taken in February 1944, showed a rate of 123, and a tendency to right axis deviation; the ST segments were depressed (digitalis) and the T-waves, although blunted, were higher than in figure 1, A. Another tracing (figure 1, C), taken on March 30, 1944, showed a rate of 105, less tendency to right axis deviation than in the previous tracing, and the T-waves were blunted in Leads I and II, and inverted in Lead III. Lead CF IV was not included in the study at this time. The basal metabolic rate was plus 17 per cent on November 11, 1944. It was not possible to obtain actual metabolic rates in the interim, because of the patient's inability to coöperate. Quinidine sulfate was effective in reducing the heart rate on several occasions. She continued to be nervous, and, although her pulse remained below 85 while at rest, excitement and effort beyond ordinary activity readily produced tachycardia, which subsided irregularly with prolonged rest.

The electrocardiogram (figure 1, D) taken January 20, 1945, showed a marked uncontrollable somatic tremor. The rate is 120 and the T-waves are distinctly higher than when the excessive doses of thyroid had been taken. The patient had been worried and overly active, when suddenly while asleep on January 28, 1945, she was seized with severe precordial pain. Examination revealed a regular pulse rate of 160, and the blood pressure was 100 mm. Hg. systolic and 62 mm. diastolic. The patient was covered with a cold perspiration, and the other physical findings were negative. The patient failed to respond to the medication, and she died suddenly two and one half hours after the onset of pain. Permission for postmortem examination could not be secured.

Comment

An exactly similar case could not be found in the literature, since this patient consumed far more thyroid than has been previously reported (Daniel, 1928).[1] No attempt could be made to compute the total amount of thyroid ingested since no regular plan was followed after the first six months. The patient, in her good mental state, had testified concerning her former excessive dosages and her statements were corroborated by estimates made from empty bottles found in her environs.

It is possible that too much conservatism in thyroid dosage has been used by the medical profession in the past. The factor of safety is large, and although exceeded in this case, it is suggested that a much higher dose (U.S.P.) may be used where the thyroid effect is desired. Further work upon the amount of thyroid necessary to increase the basal metabolic rate would seem to be in order to establish effective, but non-toxic dosage levels.

The electrocardiogram taken during the first week of hospitalization showed flattened T-waves. Immediately preceding this, 100 grains of thyroid had been ingested daily for at least one week. In later curves, the T-waves are more upright, which becomes apparent when the error in standardization is taken into consideration. Hoffman,[2] in 1914, first commented on high T-waves in hyper-

thyroidism, believing that height paralleled pulse rate. Krumbhaar [3] confirmed these findings in 1918. White and Aub,[4] in the same year questioned this correlation. Pardee,[5] in 1928, confirmed the findings of high T-waves in hyperthyroidism, whereas Lewis,[6] in 1923, refuted them. Willius [7] noted high T-waves in thyrotoxicosis and Hamburger [8] noted high T-waves in several cases but without relation to the patient's condition or basal metabolic rate; Dow and Langley [9] in 1932, and McGuire and Foulger,[10] in the same year, gave similar opinions. The findings in this case report might indicate that the amplitude of the T-waves is decreased by thyroid feeding. Definite conclusions concerning T-wave involvement in thyroid feeding and thyrotoxicosis must await further study.

Summary

A case is reported in which huge doses of thyroid extract were ingested.

The weight loss amounted to more than half of the initial weight recorded; from 166½ lbs. (75.6 kg.), to 80 lbs. (36.3 kg.).

Electrocardiographic study at the height of thyroid feeding revealed T-waves of definitely decreased amplitude, and as the thyroid was withdrawn, the T-waves increased in amplitude.

The patient, prior to death, was in a normal mental state, and retained as her only obvious residue, an unstable vascular system, manifested by a sinus tachycardia which developed upon extraordinary activity.

BIBLIOGRAPHY

1. Daniel, W. W.: The deleterious effects of indiscriminate use of thyroid preparations in obesity, Jr. Med. Assoc. Georgia, 1928, xvii, 192.
2. Hoffman, A.: Die Electrokardiographie, 1914, J. F. Bergmann, Wiesbaden, p. 108.
3. Krumbhaar, E. B.: Electrocardiographic observations in toxic goiter, Am. Jr. Med. Sci., 1918, cxcv, 175.
4. White, O. D., and Aub, J. C.: The electrocardiogram in thyroid disease, Arch. Int. Med., 1918, xxii, 766.
5. Pardee, H. E. B.: Clinical aspects of the electrocardiogram, 1924, Paul B. Hoeber, p. 162.
6. Lewis, T.: Clinical electrocardiography, Ed. iii, p. 117, 1925, Shaw, London.
7. Willius, F. A.: Clinical electrocardiograms—their interpretation and significance, 1929, W. B. Saunders Co., Philadelphia, p. 159.
8. Hamburger, W. W., Lev, M. W., Priest, W. S., and Howard, H. C.: Changes in T-waves of the human electrocardiogram following iodine medication, and thyroidectomy, Arch. Int. Med., 1929, xliii, 35.
9. Dow, C. S. D., and Langley, G.: Some aspects of the electrocardiogram in toxic goiter, Quart. Jr. Med., 1932, i, 9.
10. McGuire, J., and Foulger, M.: Influence of thyroid extract and hyperthyroidism on the electrocardiogram with special reference to the T-waves, Am. Heart Jr., 1932, viii, 114.

PNEUMOCOCCIC MENINGITIS SUCCESSFULLY TREATED WITH PENICILLIN AND SULFADIAZINE*

By JAMES S. SWEENEY, Colonel, MC, AUS, F.A.C.P., and JOHN T. LESLIE, Major, MC, AUS, *Brigham City, Utah*

THE prognosis in cases of pneumococcic meningitis has improved considerably since the advent of the sulfonamides and still more so since penicillin.[1, 2, 3, 4, 5, 6, 7, 8] The mortality rate, however, continues to be quite high. Very few individual cases or series of cases treated with penicillin or penicillin and sulfa drugs have been reported. It is anticipated that as more cases are reported and thus more experience gained, further improvement in methods of treatment will follow and in turn a material reduction will result in both mortality and morbidity.

CASE REPORT

A 22 year old white soldier sustained a .25 in. calibre gun shot wound of the face on July 11, 1944 when hit by a sniper's bullet. The entrance of the bullet was through the left temporal fossa and its exit was through the right nasal bone. It resulted in destruction of the left eye, compound, comminuted fractures of the left maxilla, orbital bones, nasal bones and nasal septum with extension of the fracture into the left frontal sinus, cribriform plate, left wing of the sphenoid and base of the left temporal bone, and a simple linear fracture of the left frontal bone. Following the injury, he was unconscious for four days. Two days after the injury a cerebrospinal fluid rhinorrhea was noted. Ten days after the injury meningitis, type undetermined, developed but promptly disappeared after penicillin and sulfadiazine were given. On August 2 enucleation of the remaining structures of the left eye was completed. A transfrontal bone flap was done on August 24 with the expectation of further operation 10 days later in an effort to stop the cerebrospinal fluid rhinorrhea. No further drainage occurred, however, after September 2. He gradually improved and, when his condition warranted it, he was evacuated to the States.

He arrived at this hospital December 29, ambulatory and in good condition except for a mild purulent conjunctivitis on the left. This was being treated symptomatically when, on January 8, 1945, he complained of headache, had a chill and a temperature elevation to 104°. He had been in the tropics in a known malarial area and this disease was suspected but several blood smears were negative. The following day he was comatose with a stiff neck and with positive Kernig and Brudzinski signs. A spinal tap revealed the fluid to be very cloudy and under markedly increased pressure. A smear of the fluid showed many gram positive diplococci resembling pneumococci and direct typing showed type 25. The cerebrospinal fluid culture, which showed profuse growth, subsequently confirmed this. On January 9, 30,000 units of penicillin were given intrathecally, 200,000 units intravenously and 6 grams of sodium sulfadiazine intravenously. On January 10, 50,000 units of penicillin were given intrathecally, 340,000 units intravenously and 6 grams of sodium sulfadiazine intravenously. Cerebrospinal fluid on this date was less cloudy but still under considerable pressure. Culture of the fluid showed only a slight growth of pneumococci. On January 11, 200,000 units of penicillin were given intravenously and 1 gram of sulfadiazine every four hours was started by nasal tube. On January 12 the cerebrospinal fluid was still cloudy. Forty-five thousand units of penicillin

* Received for publication April 9, 1945.
From Bushnell General Hospital.

were given intrathecally and 25,000 units intramuscularly were started every three hours. On this date the patient was still comatose and appeared considerably worse. A frontal temporal trephine was done by Major Max T. Schnitker, MC, AUS, Chief of Neurosurgical Section, in an effort to locate an extradural or frontal lobe abscess or focus. No abscess was found. During the operation, 50,000 units of penicillin were instilled into the left lateral ventricle. The patient's condition continued unchanged after the operation. He remained unconscious and totally unresponsive until January 14 when he suddenly roused from his coma, asked for a bed pan and shortly afterward wanted to discuss a furlough. On this date, after he had come out of his coma another 50,000 units of penicillin were instilled into the left ventricle. Following this he improved rapidly and had no apparent residual ill effects from his illness. Twenty-five thousand units of penicillin were given intramuscularly every three hours and 1 gram of sulfadiazine every four hours until February 4 at which time the cerebrospinal fluid cell count had returned to normal. Culture of the fluid was negative on and after January 12. Blood culture taken on January 9 was negative. Penicillin was instilled into the left orbital fossa throughout the illness. The patient received a total of 5,665,000 units of penicillin and 165.5 grams of sulfadiazine.

Comment

A mild conjunctivitis of the injured side existed at the time of admission to this hospital but there was no apparent break in the continuity of the tissues. The possibility of osteomyelitis of the damaged bony structures was considered, but could not be demonstrated. Meningitis occurred shortly after the injury and was supposedly cured by penicillin and sulfadiazine. However, the multiple fractures involving the nose, sinuses, and orbital structures, particularly in view of the cerebrospinal fluid rhinorrhea following the injury, may well have afforded a focus where the infection was dormant for many months.

The authors felt reluctant to do a trephine in the absence of any localizing neurological signs. However, since the patient's condition was very serious and there was a possibility of an abscess in the silent area of the frontal lobes, it was considered indicated. On the day of operation a spinal tap revealed that the cerebrospinal fluid contained a few flecks of fibrin which came through the needle with difficulty. It is quite possible that there was a blockage of the cerebrospinal fluid. At the time of the trephine penicillin was instilled into the ventricle and this may have been sufficient to have relieved any blockage which might have been present. However, culture of the ventricular fluid was sterile. Neurological complications [9, 10] have been reported from intrathecal and intraventricular penicillin. This patient received the drug intravenously, intramuscularly, intrathecally and intraventricularly without any untoward effects, and although he was unconscious for five days, no residual neurological abnormalities were observed.

With large doses of penicillin given by other routes a sufficient amount may reach the cerebrospinal fluid [11] to warrant less frequent intrathecal injections, thus lessen the possibility of neurological complications.

Sulfadiazine was given concurrently with penicillin but it is believed that this patient's recovery would not have occurred without penicillin. The optimum dosage of penicillin has not been determined. However, it is more desirable to err on the side of overdosage than underdosage. The cerebrospinal fluid was sterile after the third day of treatment but in the absence of untoward reactions

and with the likelihood of relapse, medication was continued until the cerebrospinal fluid cell count returned to normal, which took a total of 27 days.

Summary

A case of pneumococcic meningitis, type 25, successfully treated with penicillin and sulfadiazine is reported.

BIBLIOGRAPHY

1. Sweet, Lewis K., Dumoff-Stanley, Edith, Dowling, Harry F., and Lepper, Mark H.: The treatment of pneumococcic meningitis with penicillin, Jr. Am. Med. Assoc., 1945, cclxiii, 263–267.
2. Litvok, Abraham M., Appelbaum, Emanuel, and Greene, Morton: Pneumococcic meningitis, Am. Jr. Dis. Child., 1944, lxvii, 485–486.
3. Harford, Carl G., Martin, Samuel P., Hageman, Paul O., and Wood, W. Barry, Jr.: Treatment of staphylococcic, pneumococcic, gonococcic and other infections with penicillin, Jr. Am. Med. Assoc., 1945, cxxvii, 325–329.
4. Dawson, Martin H., and Hobby, Gladys L.: The clinical use of penicillin, Jr. Am. Med. Assoc., 1944, cxxiv, 611–622.
5. Evans, Albert L.: The treatment of intracranial infections with penicillin, Jr. Am. Med. Assoc., 1944, cxxiv, 641–643.
6. Waring, Antonio J., Jr., and Smith, Margaret H. D.: Combined penicillin and sulfonamide therapy in the treatment of pneumococcic meningitis, Jr. Am. Med. Assoc., 1944, cxxvi, 418–424.
7. Rosenberg, David H., and Arling, P. A.: Penicillin in the treatment of meningitis, Jr. Am. Med. Assoc., 1944, cxxv, 1011–1017.
8. Cairns, H., Duthie, E. S., Lewin, W. S., and Smith, Honor V.: Pneumococcal meningitis treated with penicillin, Lancet, 1944, i, 655.
9. Ruegsegger, James M.: Pneumococcal meningitis, Ann. Int. Med., 1942, xvii, 693–721.
10. Johnson, Herbert C., and Walker, Earl A.: Intraventricular penicillin, Jr. Am. Med. Assoc., 1945, cxxvii, 217–219.
11. Cooke, Jean V., and Goldring, David: The concentration of penicillin in various body fluids during penicillin therapy, Jr. Am. Med. Assoc., 1945, cxxvii, 80–87.

SPONTANEOUS RUPTURE OF THE SPLEEN DURING MALARIA THERAPY; REPORT OF A CASE*

By Lawrence I. Kaplan, Capt., Hilton S. Read, Lt. Col., F.A.C.P., and Dewitt F. Mullins, Capt., M.C., A.U.S., *Thomasville, Georgia*

The rarity of spontaneous rupture of the spleen in naturally acquired malarial infections has been expressed by Manson-Bahr,[1] Stitt,[2] and Osler.[3] Since the introduction of malaria as a therapeutic agent in the management of neurosyphilis, 31 cases of splenic rupture during treatment have been reported in the literature, either in detail or as personal references. Since this total cannot include unreported cases and cases that have not been recognized, the incidence of the complication probably approaches at least twice that number. Only one

* Received for publication July 16, 1945.
From Finney General Hospital.

known case of recovery has followed splenectomy.[4] In view of the gravity and unpredictability of this almost instantaneously fatal complication, it is felt that the addition of this case report will serve once again to remind clinicians of this unfortunate occurrence during a therapeutic procedure.

Cantacuzene,[5] Claude,[6] Weygandt,[7] Krumbhaar,[8] Herzig,[9] and Beckman [10] each vaguely referred to single cases of fatal splenic rupture encountered during the therapy of neurosyphilis. DeAsis [11] found two cases with ruptured spleens in a review of 101 cases of induced malaria, but full descriptions were never submitted. Bruetsch [12] reported the case of a 61 year old paretic who, following the fourth vivax paroxysm, suffered abdominal pain and circulatory collapse with death ensuing 24 hours after the onset of symptoms. At autopsy a 6 cm. tear was found along the lower margin of the spleen. Wile and Mundt [13] reported a single instance of splenic rupture in a series of 1026 cases. Their patient developed sudden cyanosis and dyspnea after the thirteenth paroxysm, and died within 45 minutes. Moore [14] reported two ruptured spleens in a series of 1600 patients treated with malaria therapy. Fong,[15] in a series of 1012 patients, encountered two cases, one occurring after the second paroxysm and the other after the eleventh paroxysm. Both spleens were enlarged, the first weighing 660 grams and the second 540 grams. Twitchell [16] reviewed the case of a 32 year old white male with general paresis who developed abdominal distention and vomiting after being placed on quinine therapy following the completion of 18 paroxysms. This patient reached operation, but died the following morning. An irregular 8 cm. tear was found in the hilus region extending inferoposteriorly. The spleen weighed 408 grams.

Polayes and Lederer [17] encountered a single fatality due to spontaneous rupture of the spleen in a 36 year old white paretic who had experienced five tertian paroxysms prior to the onset of stupor, dysarthria, inability to elevate the eyelids, tremor of the tongue and rather deep cyanosis. No local signs suggestive of abdominal hemorrhage existed and the cyanosis was thought to be the result of a pneumonic process also present. Autopsy revealed a spleen weighing 310 grams with several large capsular rents, the largest one measuring 6 cm. in length and extending deep into the pulp. These authors also abstracted the case reports of Alexander,[18] Hermann,[19] Tromner,[20] Bachmann,[21] Harris,[22] Clark,[23] and Robbins.[24] These seven fatalities occurred during induced vivax malaria, and the onset of collapse varied from the second to the tenth paroxysms. The remaining reports have been made by Jutz and Jacobi,[25] Adelheim (two cases),[26] Buttner and Hauer,[27] Jacobi and Herholz,[28] Palmgren,[29] Duprez,[30] and Currado.[31]

In Dattner's [32] review of over 5,000 cases treated in the Jauregg clinic, not a single case of spontaneous rupture of the spleen is reported. Although he feels that the arbitrary limit of eight malarial paroxysms used in their series may have accounted for the absence of this complication, at least nine of those reported in the literature developed before the eighth paroxysm.

Case Report

History. A 38 year old white private was admitted to the Neurosyphilis Service January 30, 1945. In November 1942 a positive blood serologic reaction was discovered at a routine pre-induction examination, although the patient had no definite

history of a primary or secondary syphilitic lesion. He completed six weeks of arsenical and bismuth antisyphilitic chemotherapy in civilian life. On induction into the Army in April 1943, a syphilis register was opened with a diagnosis of neurosyphilis manifested by positive blood and spinal fluid serologic reactions. Over an irregular period of 10 months in the Army, the patient received a total of two neoarsphenamine, 36 mapharsen, and 16 bismuth injections. In May 1944, in Calcutta, India, a positive blood and spinal fluid serologic reaction was again discovered and

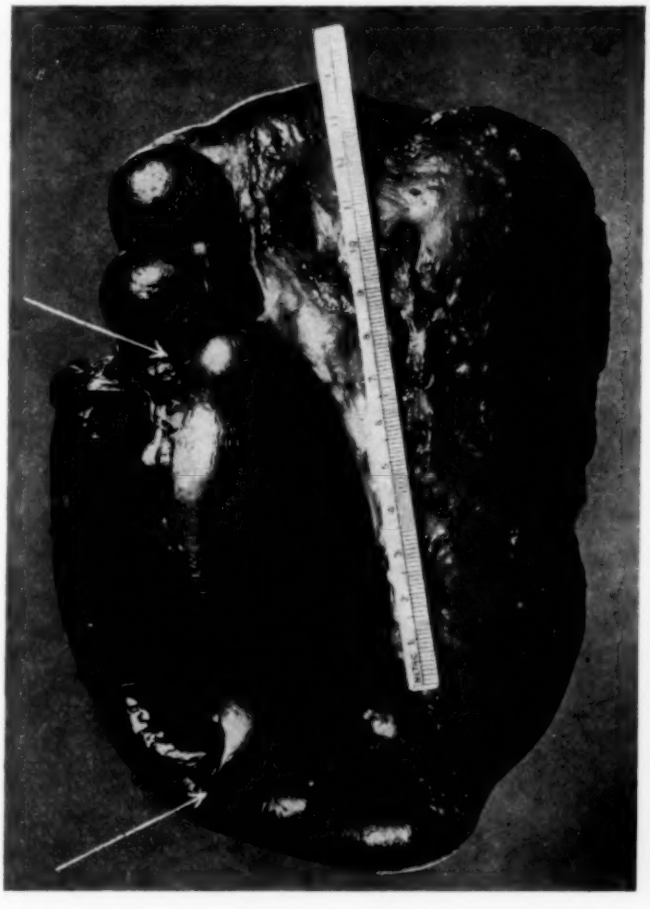


FIG. 1. Spleen, postero-medial aspect, showing spontaneous rupture. The extent of the 8 cm. laceration is marked by two arrows. Clotted blood can be noted between its margins.

he received eight injections of bismuth before returning to duty. He was rehospitalized in November 1944 for the completion of dental work. Blood and spinal fluid reactions were again found to be positive and he was finally evacuated to the Zone of the Interior for further evaluation and therapy. He had had gonorrhea at 16 years of age (1927). In the summer of 1944, while in India, he had an attack of malaria and received both quinine and atabrine for one week. He had no further malarial recurrences.

On admission, the patient complained only of difficulty in walking in the dark

and the occasional sensation of not knowing where his feet were. He had had headaches and dizziness while working in the sun, but had no history of cardiac, kidney or liver disease. General physical examination was essentially within normal limits. The spleen was not palpable.

Neurological Examination. Pupils reacted equally to light and accommodation; fundi were normal bilaterally. Deep tendon reflexes in the lower extremities were hypoactive and there was a loss of deep pain sensibility and diminution in vibratory sensation in both lower extremities. The remainder of the neurologic and psychiatric examinations was within normal limits.

Course. Blood serologic tests January 31, 1945 revealed a positive Kahn reaction. Spinal fluid examination January 31, 1945 revealed a positive Wassermann reaction in 0.1 c.c. dilution with 13 white blood cells per cubic mm., 68.2 mg. per cent total protein and a colloidal gold curve of 3443210000. Electrocardiogram and chest roentgenogram were normal and the remainder of the laboratory examinations were within normal limits.

Because of this patient's history of previous natural malaria in India, he was inoculated February 6, 1945 with the DuBose strain of Southwest Pacific vivax malaria. Following a pre-patent period of four days and an incubation period of five days, he developed a quotidian malarial cycle with an early remittent type of temperature. His course was uncomplicated until the onset of his twelfth paroxysm on February 23, 1945. At 12:00 noon February 23, 1945, the patient complained of a moderate aching pain over the precordium and the left anterior chest wall with no radiation to arms or abdomen. He had a severe malarial rigor at 12:10 p.m., and at 2:30 p.m., following the completion of his chill, he became mildly dyspneic, but extremely restless and delirious. His pulse rate was 144, blood pressure 70 mm. Hg systolic and 45 mm. diastolic, heart sounds fair, chest clear, except for a few râles at the right base posteriorly. The abdomen was soft. The liver and spleen were not palpable, and no edema was present. His temperature was 103.8° F., although all four extremities were cold and clammy. He received ⅙ grain of morphine and an oxygen mask was applied. During the next 15 minutes his status deteriorated rapidly. The blood pressure could not be recorded and the pulse rate was 150 to 160 with fair heart sounds. Respirations increased to 40 per minute and then became Cheyne-Stokes in nature. Artificial respiration aided by an oxygen tent was of no avail. He had received 0.2 gram of thio-bismol at 2:35 p.m. intramuscularly in an effort to interrupt his next paroxysm, and a plasma transfusion was being started when the patient died at 3:05 p.m. February 23, 1945. Respirations ceased shortly before the heart beat. An electrocardiogram taken one hour before death revealed no changes other than a marked sinus tachycardia.

Summary of Necropsy Findings (Necropsy performed by D.F.M.): The immediate cause of death was exsanguination and circulatory failure resulting from spontaneous rupture of the spleen. The underlying cause of death was therapeutic malaria administered in the treatment of tabes dorsalis.

Spleen: Weight 675 gm. after removal. The capsule showed two irregular linear vertical lacerations (figure 1). One tear was on the lateral convex surface measuring 8 cm. in length and the other on the medial concave surface measuring 4 cm. covered with a dark red, currant jelly, blood clot. Blood clot separated the capsule from the underlying splenic tissue at the edges of the lacerations. The capsule was thin, the edges rounded. The consistency was soft and markedly friable. The spleen was dark, reddish-blue in color. The cut surface was coarsely granular, dark-red and diffluent in appearance. The pulp was exceedingly friable. Microscopic examination showed the tear of the capsule with hemorrhage. The capsule was very thin. The malpighian bodies and trabeculae were widely separated, resulting from the marked proliferation of reticuloendothelial cells of the red pulp and

congestion of the sinusoids with red blood cells and mononuclear cells. The sinusoids were lined by large endothelial cells with enlarged, elongated nuclei. They contained many mononuclear histiocytic cells displaying ameboid shapes containing clear vacuoles and some dark brown granular malaria pigment. The malpighian bodies were compressed and the germinal centers were small. Large foci of interstitial hemorrhage with coarse hemosiderin deposits were noted throughout the splenic pulp. Neutrophiles were rare. The endothelial lining of the small veins showed marked swelling and in some areas subintimal infiltration of mononuclear histiocytes, lymphocytes and plasma cells.

Numerous red blood cells showed *Plasmodium vivax* parasites in ring and schizont stages of development after staining in 4 per cent Giemsa stain overnight.

Liver: Weight 2100 gm. The surface was dark, reddish-tan and finely granular. The edges were rounded. On section the cut surface was dark, reddish-tan in color and was more friable than normal. The normal hepatic pattern was present on microscopic examination but there was moderate thickening of the periportal connective tissue with infiltration by many round cells and occasional histiocytes. The Kupffer cells were swollen and contained reddish-brown granular pigment. The hepatic cells showed cloudy swelling and finely granular yellowish-green pigment in their cytoplasm. Occasional foci of interstitial hemorrhage were present. The small bile ducts appeared normal. The portal veins contained several mononuclear cells.

Lungs: The right lung weighed 300 gm., the left lung 320 gm. Both lungs showed a moderate amount of coal pigment. The upper lobes contained a moderate amount of frothy pink fluid. Both lower lobes showed moderate atelectasis.

Heart: Weight 275 gm. Essentially normal except for pale color.

Pancreas: Weight 100 gm. Essentially normal.

Adrenals: Normal in size and shape and location. The right adrenal was covered with some clotted blood but on section appeared normal. Microscopic examination showed marked congestion of the vessels of the cortex.

Kidneys: The right kidney weighed 140 gm., the left kidney 150 gm. Gross examination essentially normal. The glomeruli appeared normal. The epithelium of the tubules displayed moderate cloudy swelling. The descending loops of Henle contained some amorphous pink-staining material. The interstitial tissue of the medulla contained numerous enlarged venules and capillaries.

Lymph Nodes: All lymph nodes showed slight generalized enlargement. On microscopic examination the reticulo-endothelial cells were increased in number and in size. The germinal centers appeared decreased in size. The sinuses were markedly dilated and contained numerous large histiocytic mononuclear cells which showed little phagocytic activity.

Brain: Weight 1340 gm. The cerebral vessels showed marked congestion. The cut surface displayed prominent congested vessels but no areas of softening or increased density. Microscopic examination displayed engorgement of the blood vessels with moderate perivascular lymphocytic and plasma cell infiltrations. The perivascular spaces were widened and contained a few histiocytic mononuclear cells. The parenchymal brain cells appeared essentially normal.

Spinal Cord: Microscopic examination revealed moderate perivascular, chronic inflammatory infiltration. There was a decrease in the cellular elements in the posterior horns with a relative increase in neuroglial tissue.

Comment

Although chronic enlargement of the spleen following recurrent attacks of natural malaria has been offered as an explanation for splenic rupture, it is

known that this complication develops much more commonly during therapeutic malaria than in the naturally acquired disease in which it rarely occurs. With the exception of the case herein reported, in which an attack of natural malaria preceded the therapeutic inoculation by approximately six months, most of the ruptures during therapy occurred in patients experiencing primary malarial attacks.

The differentiation between traumatic and spontaneous rupture of the spleen in malaria-treated cases is often difficult to evaluate because so many of the patients are restless and disturbed during treatment, incurring minor injuries probably sufficient to cause rupture in an enlarged spleen pathologically altered by the malarial process. Trauma could not be indicted as an etiological factor in this case report, unless the severe malarial rigor followed immediately by collapse be considered the equivalent of a traumatizing incident. Nevertheless, patients receiving malarial therapy should be handled with extreme caution in an effort to prevent even insignificant injury to the chest or abdomen.

Polayes and Lederer [17] are of the opinion that the increase in fibrous tissue in the splenic capsule and septa with resultant loss of elasticity, as reported by Bigland [33] and his associates in more than 97 per cent of 390 cases of syphilis of the central nervous system, predisposes to spontaneous rupture. The usual changes considered as predisposing factors, namely enlargement and softening, were not present in the spleens of patients suffering from neurosyphilis prior to the induction of malaria, according to these authors. The necropsy findings in several of the 31 cases of spontaneous rupture reviewed above revealed thickened splenic capsules partly adherent to the diaphragm in some cases, and merely firm and brittle in others. In Bruetsch's case,[12] one portion of the capsule was actually the seat of cartilaginous changes. Therefore, it seems rather likely that fibrosis and thickening of the splenic capsule, whether occasioned by a syphilitic process or by repeated attacks of malaria, act to restrain the splenic expansion which normally occurs during malarial infection as a result of the destruction of erythrocytes and proliferation of the reticulo-endothelial system. Since this expansion can only take place where normal elasticity remains, rupture in some cases may, therefore, depend upon the degree of engorgement, precipitated perhaps by the added insult of some injury.

Summary

1. A case of spontaneous rupture of the spleen during vivax malaria therapy in a patient with early tabes dorsalis is reported.

2. Reports of 31 similar cases of spontaneous splenic rupture, appearing in the literature, are mentioned.

3. Etiological factors are briefly considered.

BIBLIOGRAPHY

1. Manson-Bahr, Philip H.: Manson's tropical diseases, 8th Edition, Revised, 1926, William Wood and Company, Division of Williams and Wilkins Co., Baltimore.
2. Strong, R. P.: Stitt's diagnosis, prevention and treatment of tropical diseases, 6th Edition in 2 vols., 1943, The Blakiston Co., Philadelphia.
3. Osler, William, and McCrae, Thomas: The principles and practice of medicine, 1922, D. Appleton-Century Co., New York.

4. VERMEYLEN, G., and VERVAECK, P.: Les formes psychosiquez chez les paralytiques généraux malarises et la notion de démence paralytique, Encephale, 1930, xxv, 563 and 643.
5. CANTACUZENE, J.: Résultats obtenus en Roumaine par la malariotherapie appliquée au traitement de la syphilis des centres nerveux, Bull. de l'Office internat. d'hyg. pub., 1928, xx, 259–268.
6. CLAUDE, H.: La malariatherapie de la paralysie générale, Rev. med. franc., 1930, xi, 121–125.
7. TROMNER, E., and BALTZER, H.: Spontaneous rupture of spleen in therapeutic malaria, Klin. Wchnschr., 1925, iv, 2159–2160.
8. KRUMBHAAR, E. B.: Diseases of the spleen, *in* OSLER, W.: Modern medicine: its theory and practice, 3rd Edition, edited by T. McCrae, 1927, Lea & Febiger, Philadelphia, vol. 5, chap. 5, p. 162.
9. Quoted by TROMNER.[7]
10. BECKMAN, T. M.: Uber spontane Milzruptur bei Impfmalaria, Acta chir. Scandinav., 1930, lxvi, 250–258.
11. DE ASIS, C.: Malaria as a therapeutic agent for paresis, Arch. Neurol. and Psychiat., 1929, xxii, 752.
12. BAHR, M. A., and BRUETSCH, W. L.: Two years' experience with the malarial treatment of general paresis in a state institution, Am. Jr. Psychiat., 1928, vii, 715.
13. WILE, J. J., and MUNDT, L. K.: Avoidance of fatal complications in therapeutic malaria, Arch. Dermat. and Syph., 1941, xliv, 1078.
14. MOORE, J. E.: The modern treatment of syphilis, 1943, Charles C. Thomas, Springfield, Illinois.
15. FONG, T. C. C.: A study of the mortality rate and complications following therapeutic malaria, South. Med. Jr., 1937, xxx, 1084.
16. TWITCHELL, E. W.: Spontaneous rupture of spleen following malaria therapy for general paresis, report of case, California and West. Med., 1930, xxxiii, 512.
17. POLAYES, S. H., and LEDERER, M.: Rupture of spleen in malarial therapy in syphilis, Jr. Am. Med. Assoc., 1931, xcvi, 1127–1129.
18. ALEXANDER, M.: Rupture of spleen from therapeutic malaria, Scalpel, May 10, 1924 (Abstract in Lancet, 1924, ii, 182).
19. HERMANN, G.: Jahresbericht über die Malariabehandlung der progressiven Paralyze der deutschen psychiatrischen Klinik in Prag, 1923–1924, Med. Klin., 1925, xxi, 395.
20. Quoted by TROMNER.[7]
21. BACHMANN, F.: Spontaneous rupture of spleen in therapeutic malaria, München. med. Wchnschr., 1926, lxxiii, 528–530.
22. HARRIS, N. G.: Case of rupture of spleen after artificial induction of malaria, Lancet, 1928, ii, 500–501.
23. CLARK, E. A.: Spontaneous rupture of spleen during therapeutic malaria, with report of case, Ontario Jr. Neuro-Psychiat., 1929, 47–50.
24. ROBBINS, F. C.: Rupture of spleen during antisyphilitic malarial treatment, U. S. Vet. Bur. Med. Bull., 1929, v, 291–294.
25. JUTZ, B., and JACOBI, A.: Spontanruptur der Milz bei Impfmalaria, München. med. Wchnschr., 1931, lxxviii, 395–396.
26. ADELHEIM, R.: Pathology of therapeutic malaria in general paralysis, Wien. klin. Wchnschr., 1926, xxxix, 412–416.
27. BUTTNER, R., and HAUER, A.: Spontaneous rupture of spleen following the use of therapeutic malaria in general paralysis, case report, Arch. f. Schiffs-u. Tropen.-Hyg., 1938, xlii, 167.
28. JACOBI, E., and HERHOLZ: Spontaneous rupture of the spleen in inoculation malaria, Klin. Wchnschr., 1932, xi, 599.

29. PALMGREN, D.: Rupture of the spleen in inoculation malaria (in gonorrhea), Acta dermat.-venereol., 1932, xiii, 471.
30. DUPREZ, C.: Death from spontaneous rupture of the spleen in general paralysis treated with malaria, case report, Scalpel, 1933, lxxxvi, 967.
31. CURRADO, C.: Spontaneous rupture of the spleen during malarial therapy, Minerva med., 1933, i, 859.
32. DATTNER, B.: The management of neurosyphilis, 1944, Grune and Stratton, New York.
33. BIGLAND, P. M., WATSON, G. A., and BIGLAND, A. D.: Relation between general paralysis and somatic syphilis, Lancet, 1924, ii, 588–593.

IDIOPATHIC DILATATION OF THE COMMON BILE DUCT WITH COEXISTENT PRIMARY HEPATIC CARCINOMA: REPORT OF A CASE *

By LOUIS P. ARMANINO, M.D., *Stockton, California*

Introduction. Two rare diseases, idiopathic dilatation of the common bile duct (choledochus cyst) and hepatic carcinoma, found in the same youth, are a unique combination. No similar case studies have been described or referred to in the medical literature. The coexistence of these abnormalities of the biliary system suggests that the choledochus cyst was the precursor of the malignancy of the liver.

A complete report of such a case with autopsy observations is presented.

CASE REPORT

First admission (July 16, 1943 to August 13, 1943). J. W. A., a 17 year old white single farm-hand, entered Vanderbilt University Hospital complaining of jaundice and swelling of the abdomen.

Present Illness. Though his older sister stated that the patient's skin had a yellowish tint when he was a small baby less than a year old, it was only in the eight years preceding admission that the patient himself noted any abnormalities. Each spring since the age of nine he had developed episodes of jaundice associated with light stools and dark urine. There was no associated pain, and these attacks lasted usually from two weeks to two months and disappeared spontaneously with no sequelae.

However, the episode starting in April, 1942 persisted throughout the entire year up to the time of entry in July, 1943. During this time he had light brown stools, dark urine, and occasionally pruritus. Two months before admission he began to feel weak, developed malaise, and gradually lost 10 pounds in weight.

Five weeks before admission to the hospital his abdomen began to swell. Two weeks later he developed abdominal pain for the first time. This was severe, localized in his right upper abdomen, lasted one day, and was relieved by codeine. His local physician told him that his liver was enlarged. For two days prior to admission the patient had constant lower abdominal pain and some difficulty getting his breath when lying flat in bed.

* Received for publication December 8, 1944.
From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee.

There had been no vomiting, tarry or bloody stools, or constipation. Eructations and a burning sensation in his "stomach" had occurred whenever he ate fatty foods during the previous several years.

Past History. The patient had had the common diseases of childhood. His habits had been regular. He very rarely drank alcoholic beverages. He was never exposed to any known harmful chemicals, nor did he use any unusual drugs.

Family History. The father, mother, and seven siblings were living and well. There were no apparent familial diseases, and no condition similar to that of the patient was known to be present in the family.

Physical Examination. Temperature 101° F. Pulse 90. Respirations 28. Blood pressure was 105 mm. Hg systolic and 75 mm. diastolic.

General Appearance. The patient was a deeply jaundiced, underdeveloped, undernourished, red-headed, freckle-faced youth of about 17 years who appeared to be chronically ill. He seemed quite uncomfortable and was propped up in bed breathing rapidly, complaining of tightness in his enlarged abdomen.

The skin was yellow in color with several scattered small excoriated areas from scratching. The head and neck were normal. There was no lymphadenopathy. The sclerae were icteric but otherwise the eyes were negative.

The thorax was symmetrical, showing poor expansion. The thoracic wall was thin and showed flaring of the lower rib margins. Both leaves of the diaphragm were high posteriorly and moved very little on deep inspiration. The area of liver dullness extended up to the level of the fourth rib anteriorly on the right side. Vocal fremitus was normal. The breath sounds were puerile. There were no râles or friction rubs. The heart was negative in all respects.

The abdomen was very protuberant, the skin being tightly stretched and containing prominent veins over its upper portion. Fluid wave and shifting dullness were present. A tender grossly lobulated liver edge of firm consistency was felt four fingers'-breadth below the right costal margin. The spleen was felt two fingers'-breadth below the left costal margin on inspiration. There were no other palpable masses or organs. The remainder of the examination was negative.

Laboratory Data. The urine was red-brown in color, with a specific gravity of 1.020. Albumin and sugar were absent, though bile was present. Urobilinogen was present in a 1:16 dilution. There were occasional white blood cells in the uncentrifuged specimen.

The cell counts were red blood cells 4,500,000 and white blood cells 13,750 per cubic millimeter. Hemoglobin was 13.0 gm. per 100 c.c. The differential count was as follows: 79 per cent polymorphonuclears, 19 per cent lymphocytes, and 2 per cent monocytes. Sedimentation rate (Wintrobe, corrected) was 36 mm. per hour and a packed cell volume of 39 per cent. Mean corpuscular volume was 86.6 cubic micra, mean corpuscular hemoglobin 28.8 micrograms, and mean corpuscular hemoglobin concentration 33 per cent.

Other blood studies were as follows: icterus index 27; serum bilirubin 6.8 mg. per cent; coagulation time 4 minutes; bleeding time 3½ minutes; total serum protein 5.74 gm. per cent (3.19 gm. albumin and 2.55 gm. globulin); non-protein nitrogen 30 mg. per cent; cholesterol 313 mg. per cent; Kahn reaction negative.

The stool was light brown in color with the presence of bile. No occult blood, parasites or ova were found.

Special Tests. A red blood cell fragility test showed a normal range for hemolysis. Prothrombin time was 45 per cent of normal. The tourniquet test indicated no increase in capillary fragility. The bromsulphonphthalein test for liver function showed a 52 per cent retention of the dye in 30 minutes. Hippuric acid test for liver function revealed a negligible amount excreted in the urine in one hour.

Ascitic fluid: This was sterile on culture. The specific gravity was 1.018. The

cell count was 6,959 with a preponderance of normal small lymphocytes and macrophages. Total protein was found to be 4.13 gm. per 100 c.c. of fluid; foam and Gmelin tests were positive for bile.

On chest fluoroscopy no pulmonary abnormalities or pleural effusions were noted. Both leaves of the diaphragm were elevated. The heart was normal.

A gastrointestinal series showed no intrinsic lesion of the duodenal cap; however, along the inferior medial aspect there was a pressure defect (possibly due to liver). The arch of the duodenum and its descending portion appeared to be widened as if a mass were interfering between the first and third portions of the duodenum. The mucosal pattern of the duodenum was normal. A flat film of the abdomen indicated general density in the upper abdomen probably due to enlarged liver and spleen.

Biliary drainage was unsuccessful.

Course in the Hospital. The day after entry abdominal paracentesis yielded 2400 c.c. of cloudy, green-yellow fluid which relieved the orthopnea and the low abdominal pain. This procedure was repeated five days later and 4600 c.c. of bile-stained fluid were obtained. In the following two weeks the patient received two liters of blood plasma and 15 c.c. of crude liver extract intramuscularly. He was also placed on a high carbohydrate, low fat, adequate protein diet with added vitamins. Twenty-five days after entry another abdominal paracentesis resulted in 4300 c.c. of bile-stained fluid. This procedure again relieved his recurrent abdominal discomfort.

Throughout his stay he had a daily fever varying from 99° to 101° F. There was little change in the size and shape of his enlarged liver and spleen. His icterus index had decreased to 9, his serum bilirubin to 2.44 mg. per cent, and his bromsulphonphthalein retention in 30 minutes was 40 per cent on the twenty-sixth hospital day. On discharge three days later his weight was 102 pounds, 17 pounds less than upon entry.

Clinical Diagnosis. Biliary cirrhosis of the liver due to repeated bouts of catarrhal jaundice.

Second admission (August 22, 1943 to death on August 27, 1943). Nine days after discharge, the patient reëntered the hospital complaining of enlargement of the abdomen and a productive cough.

Interval Note. The patient developed increasing anorexia and nausea. He vomited a couple of days after being home. His abdomen again started to swell, and he developed an aching pain in his left upper abdomen, just to the left of his umbilicus. Three days before reëntry he developed a productive cough, but no hemoptysis or pleuritic pain. He developed malaise and thought that he had a fever. He noted that an area over his enlarged liver had suddenly become more prominent and was tender to touch.

Physical Examination: Temperature 100.8° F. Pulse 140. Respirations 36. Blood pressure was 90 mm. Hg systolic and 60 mm. diastolic.

General Appearance: He was an acutely ill, cyanotic, dyspneic, emaciated youth with an anxious facial expression, coughing frequently. The skin was yellow in color with a loss of normal subcutaneous fat and very dehydrated.

Examination of the lungs showed vocal fremitus to be increased over both lung bases posteriorly. There was dullness over the same areas with bronchial breath sounds. Harsh bronchovesicular breath sounds were heard everywhere. Coarse moist râles were heard over both lungs posteriorly, and a friction rub was present over the left lower chest anteriorly and laterally.

The abdomen was distended with fluid and, as before, an enlarged liver was palpated four fingers'-breadth below the right costal margin. A large nodule about 8 cm. in diameter was felt in its lower border in the mid-epigastrium. The spleen was felt at the left costal margin.

Except for cyanosis of the nail beds the remainder of the examination was negative.

Laboratory Data. The urinary findings were the same as before.

The blood counts were red blood cells 4,600,000 and white blood cells 23,700 per cubic millimeter. The hemoglobin was 14.2 gm. per 100 c.c. The differential count was as follows: 85 per cent polymorphonuclears (81 per cent segmented, 3 per cent non-segmented, and 1 per cent basophiles), 11 per cent lymphocytes, 2 per cent monocytes, and 2 per cent smudges.

Other blood studies were as follows: icterus index 12; serum bilirubin 2.9 mg. per cent; non-protein nitrogen 41 mg. per cent; total serum protein 5.73 gm. per cent (3.12 gm. per cent albumin and 2.61 gm. per cent globulin).

In the stool bile was present, but no occult blood, parasites or ova were found.

The sputum was mucoid and without acid-fast bacteria. Culture revealed pneumococci, *Staphylococcus aureus,* and non-hemolytic streptococci.

Roentgenologic examination of the chest showed extensive exudation and partial consolidation which almost completely obliterated both lung fields.

Course in the Hospital. After an abdominal paracentesis removed 3500 c.c. of bile stained fluid from the abdomen, the patient was started on sulfadiazine and was placed in an oxygen tent. He was given a 500 c.c. plasma transfusion the second day. His temperature varied between 99° F. and 101.2° F., and his pulse and respirations remained fast over the next four days. During this time the mass felt in the liver continued to enlarge rapidly and caused the patient much pain locally. He gradually grew worse and died on the fifth hospital day.

Diagnoses. Biliary cirrhosis of the liver, possible primary carcinoma of the liver, pneumonia.

Postmortem Examination (By Dr. James N. Owens, Jr.): The autopsy was begun one and one-half hours after death on the body of a fairly well developed but cachectic male which appeared older than the stated age. The skin color was yellow, the lower costal margins were symmetrically flared outward, and the abdomen was large and tense. After the usual incision was made, the following observations were made:

Peritoneal cavity. This was filled with about 2500 c.c. of icteric fluid. There were numerous fibrinous adhesions between the liver and the anterior parietal peritoneum. Numerous umbilicated nodules were present on the peritoneum of the anterior abdominal wall and along the course of the pancreatic lymphatics as well as the mesenteric attachments of the stomach. The omentum was studded with similar nodules. The liver was roughly nodular and extended 10 cm. below the right costal margin at the anterior axillary line and 6 cm. below the left costal margin at the left anterior axillary line. There was a large ovoid semifluctuant whitish-gray mass present beneath the head of the pancreas so that the latter was compressed about this mass. The remaining organs were normally disposed.

Pleural cavities. No free fluid was present. Numerous small yellow-white nodules were scattered over the right parietal pleura. The left pleural cavity showed fibrin deposited over all its surfaces.

Pericardium and heart. Normal.

Lungs. The right lung weighed 1130 gm., the left 1500 gm. Numerous small, whitish, reticulated lines were seen beneath the pleura as well as numerous raised, spherical, yellow-white to brown nodules several millimeters in diameter. The parenchyma of both lungs was diffusely infiltrated with white-yellow tumor tissue (figure 1).

Gastrointestinal tract. This was normal. The opening from the biliary tract into the Ampulla of Vater was patent as was demonstrated by pressure on the gall-bladder. The region between the gall-bladder, duodenal cap, and transverse colon was occupied by a large mat of fibrous tissue.

FIG. 1. Section through left lung which is diffusely infiltrated with tumor tissue.

Liver and associated structures. The liver was enlarged and together with the stomach, extrahepatic biliary tract, duodenum and pancreas weighed 4120 gm. Several white-yellow, irregular, umbilicated tumor nodules were seen on its surface, most being on the left lobe. A large tumor mass 10 cm. in diameter occupied most of the quadrate

lobe adjacent to the falciform ligament. This projected up 2 cm. above the surrounding liver tissue anteriorly. On sectioning the liver it was observed that the major intrahepatic bile ducts were dilated to over 3 cm. in diameter and their walls were thickened. A spherical, enlarged, cystic common bile duct measuring 13 cm. in diameter was fluctuant to palpation, was externally a yellow-brown color, and was encircled by the duodenum (figure 2). When incised, a large quantity of dark green viscid bile escaped. Its wall was white and fibrous, measuring 2 to 3 mm. in thickness. The two hepatic ducts were dilated to about 15 mm. in diameter and communicated freely with the dilated common duct. There were a small fold and a dimple on the

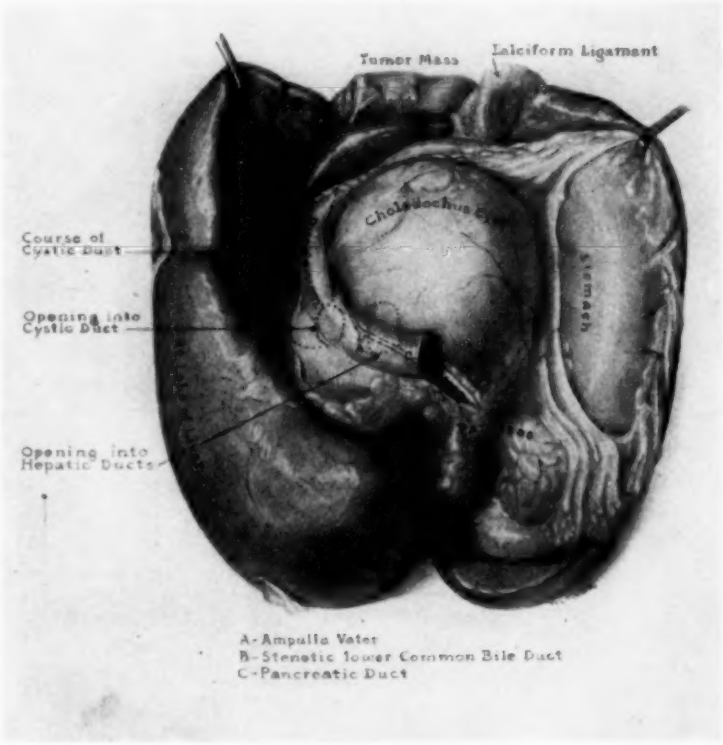


FIG. 2. Inferior view of liver and associated structures showing relations of the choledochus cyst.

inner lining of the cyst adjacent to the second portion of the duodenum. A probe could be passed through this into a 3 cm. tract where it emerged through the Ampulla of Vater into the duodenum. After this tract was opened, another duct was observed coming in from the mass of pancreas. This duct was patent and opened into the upper portion of the relatively narrow stem of the dilated common duct just outside the large cyst wall. The gall-bladder wall was thick, friable, yellow-white in color, and fungating in character. The size of the organ was normal, and its mucosa showed no areas of ulceration. The cystic duct leading to the dilated common duct was dilated to about 12 mm. in diameter with walls 3 to 4 mm. thick (figure 3).

Spleen. This was enlarged weighing 350 gm. Its consistency was soft, and its capsule was covered with fibrin.

Pancreas. This was removed with the liver and associated structures. It was flattened and intimately related to the wall of the cystic common bile duct. The ducts were not abnormal. Around the tail was a small rim of tumor tissue.

Adrenals, kidneys, ureters, bladder and internal genitalia. Grossly normal.

Microscopic Examination: Heart and aorta were normal.

Lungs (figure 4 a). The endothelial-lined subpleural lymphatics were filled with clumps and strands of irregular sized and shaped cells which were quite large. Their cytoplasm was eosinophilic and granular. The nuclei were large, spherical to ovoid in shape, with irregularly distributed chromatin. Many mitotic figures were seen as

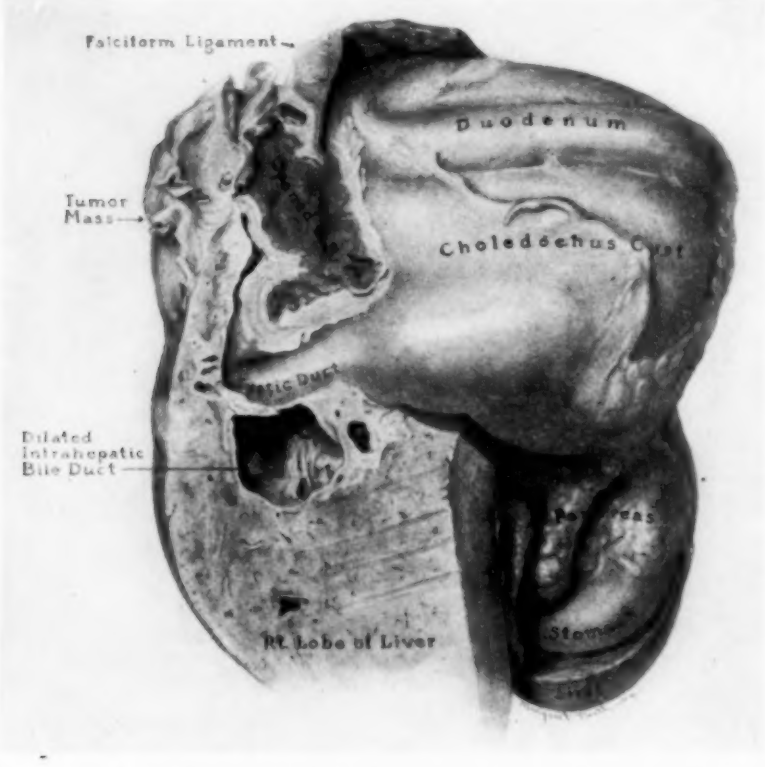


FIG. 3. Right lateral view of the sectioned liver showing the relations of the choledochus cyst, dilated cystic duct, and opened gall-bladder. Note the dilated intrahepatic bile duct.

well as a few multinucleated tumor cells. Similar tumor cells were seen distending alveoli and bronchi. Scattered throughout the neoplastic tissue and thickened alveolar walls were numerous polymorphonuclear leukocytes and lymphocytes. Occasionally a single bizarre shaped tumor cell with a mitotic nuclear figure was seen free in the lumen of a distended blood vessel. Alveoli not distended with tumor cells were filled with granular pink-staining amorphous material and large mononucleated cells. Hilar and paratracheal lymph node sections revealed masses of tumor cells similar to those seen in the lungs. In some regions central necrotic cellular debris was seen, and occasionally the tumor cells occurred in very small clumps which greatly resembled bile canaliculi. These were surrounded by dense collagenous connective tissue which was

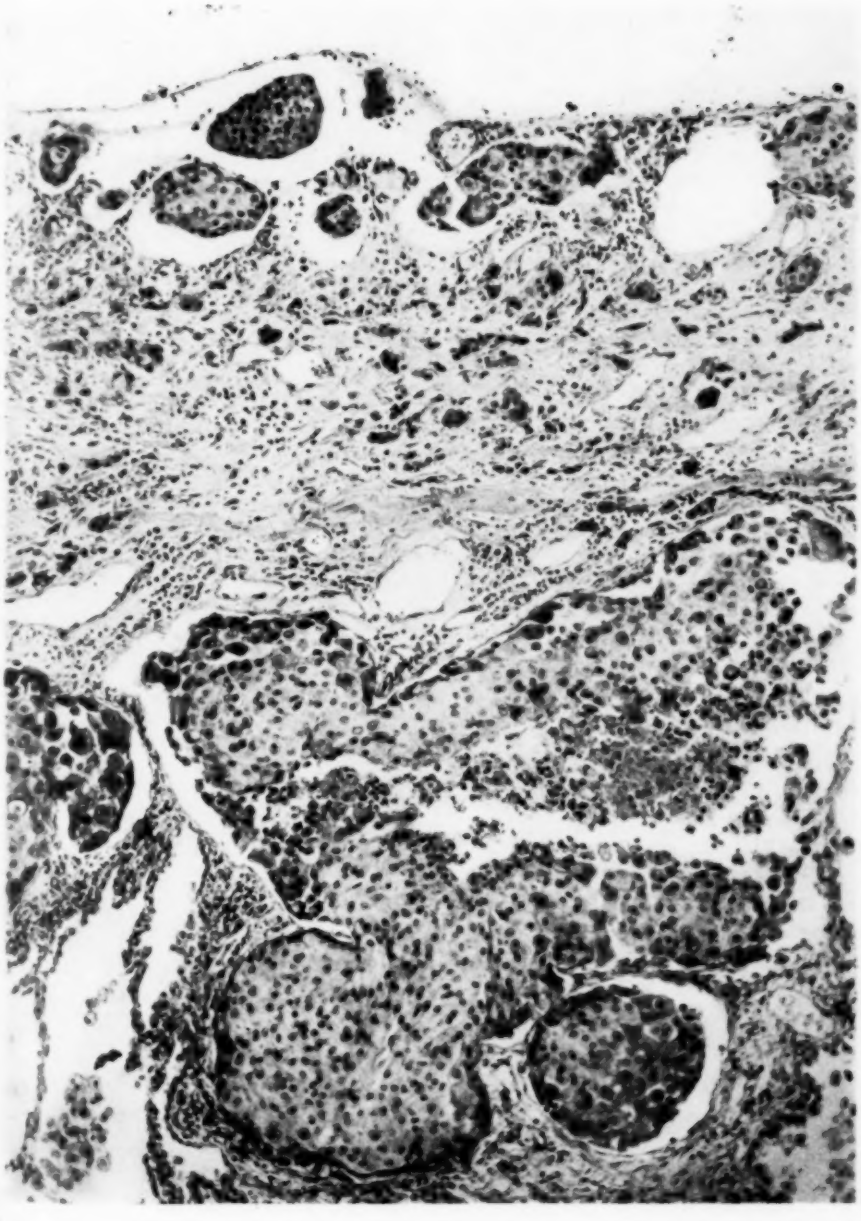


FIG. 4 a. Microscopic section (120 ×) through edge of right lung showing tumor cells in the subpleural lymphatics on the right and tumor tissue distending alveoli on the left.

infiltrated with lymphocytes, plasma cells, and an occasional eosinophile. No evidence of secretory activity was seen in these tumor cells.

Gastrointestinal tract. The subserosal layers were thickened with connective tissue proliferation. Lymphocytes, plasma cells, and clumps of tumor cells were also noted. The serosa was layered with a few areas of fibrinopurulent exudate, and it showed in other areas hyperplastic serosal cells. An omental nodule showed a wild growth of tumor cells.

Liver (figure 4 b). Over the capsule were numerous nodules of fibrous tissue in which clumps of tumor cells were seen. The central portions were mostly necrotic. Around the nodules were accumulations of plasma cells and lymphocytes. The liver parenchyma was almost entirely replaced by wildly growing tumor cells with some fibroblastic proliferation through it. The tumor seemed to be more predominant in the portal areas. Many central veins were partially or totally occluded by well laminated thrombi with early organization. Large areas of hepatic necrosis infiltrated with polymorphonuclear leukocytes were seen in some places. In other regions there was intercellular edema of the liver cells. An occasional dilated columnar epithelially lined channel was observed and was thought to be a dilated biliary duct.

Gall-bladder. The mucosa contained many large lipoid-laden mononuclear cells as well as clumps of tumor cells. The muscular layer was hypertrophied and infiltrated with neoplastic cells. In addition to tumor cells the subserosa contained lymphocytes, plasma cells, and fibrin.

Cystic common duct. A few patches of pseudostratified columnar mucus-secreting epithelial cells lined the cyst. Its wall was formed by a dense thick zone of hyalinized connective tissue.

Spleen. The capsule and trabeculae were normal. The sinusoids were distended with many red blood cells and collections of polymorphonuclear leukocytes. The lymphoid follicles were normal.

Pancreas. The overlying serosa showed the peritoneal reaction and tumor implantation previously described under gastrointestinal tract. There was moderate inter- and intralobular fibrosis with lymphocytic and plasma cell infiltration. The acini were dilated as were a few ducts. Many of the latter were obstructed with polymorphonuclear leukocytes. A few areas of fat necrosis were seen.

Adrenals. Aside from acutely engorged blood vessels and a moderate amount of pericapsular hemorrhage, these glands were not unusual.

Kidneys. The convoluted tubular epithelium showed marked cloudy swelling, but no other abnormalities were seen.

Urinary bladder, prostate, and testicle. These all appeared normal.

Final Diagnoses: 1. Idiopathic dilatation of the common bile duct. 2. Carcinoma, probably hepatic in origin, with extension to peritoneum, omentum, liver, and gall-bladder and with metastases to lungs and tracheobronchial lymph nodes. 3. Acute splenitis. 4. Acute and chronic pancreatitis. 5. Fat necrosis of pancreas.

Discussion

Idiopathic or congenital dilatation of the common bile duct is a condition of uncertain etiology. Zinninger and Cash [1] reported 82 cases in the literature up to 1932, and Shallow, Eger, and Wagner [2] more recently added 93 cases, making a total of 175 cases up to 1943. Though a long list of possible etiological factors has been proposed, that of Yotuyanagi [3] seems to be most widely accepted at the present time. His theory which is based on accepted embryologic studies explains choledochus cyst formation quite satisfactorily. He believes that cystic dilatation of the common bile duct may be due to an unequal rate of epithelial cell proliferation at the stage when the primitive choledochus is still a solid mass.[4]

FIG. 4 b. Low-power section (40×) of liver showing tumor tissue growing in the portal spaces and areas of hepatic necrosis.

Thus, if there is an increase in proliferation of the cells of the upper portion of the common duct anlage during the stage of physiologic occlusion, and a diminished proliferation in the lower portion at the same stage, when recanalization occurs at a later stage, the upper portion of the duct will be abnormally large and the lower portion relatively small. In the case reviewed in this paper one wonders how great a part increase in pressure in the biliary tract due to the stenotic lower end of the common bile duct played in ballooning out the upper cystic portion.

In this case the presence of a choledochus cyst was not suspected during life. Though the patient had repeated episodes of jaundice since early childhood, he had but a single attack of upper abdominal pain and no palpable subhepatic mass on physical examination. Apparently the downward enlargement of the hepatic lobes was sufficient to prevent the palpation of the dilated common duct. According to the analysis of Shallow, Eger, and Wagner the diagnostic triad in their 175 cases was as follows:

1. Right upper abdominal tumor (77 per cent of their cases)
2. Recurrent bouts of jaundice (70 per cent)
3. Associated abdominal pain (59 per cent)

The correct diagnosis was made or suspected in only 22 or 12.6 per cent of the cases. The disease seems to be essentially one of childhood and early adulthood,[5] and it is more prevalent in the female sex.

Obstruction of the normal flow of bile into the small intestine produces variable changes in the biliary tree and in the liver. Apparently these changes are not uniform and depend on the degree and the length of time of obstruction. Associated anatomic factors found with choledochus cysts usually cause some degree of obstruction. In this case there was a marked dilatation of the major intrahepatic biliary ducts, the hepatic ducts, and the cystic duct together with gross thickening of their walls. The liver was edematous, had numerous areas of focal necrosis, had a certain degree of cirrhotic change, and had malignant tumor tissue growing in it.

It is the latter fact which is of particular interest because of its rarity. Even when unassociated with cystic dilatation of the common bile duct, malignant hepatomata are very uncommon in the white race, especially in the younger age groups. In this case it was not possible to say definitely whether the neoplasm arose in the liver parenchyma itself or in the biliary tree. The histological type of cell present in the tumor was not characteristic, but in some areas of metastases the tumor cells occurred in very small orderly clumps which greatly resembled bile canaliculi. Ewing[6] states that though typical liver-cell tumors and typical bile-duct neoplasms cannot be readily confused, there are still many structures of uncertain significance resulting probably from a growth derived from both of these elements. Therefore, an intermediate group of mixed epithelial hepatic tumors is in evidence. Moreover, according to Ewing some cases of homogeneous type, and evidently single origin, are so far removed from the usual morphology that doubt must remain regarding their true origin.

It seems reasonable that if this patient had not had a choledochus cyst with resultant changes in his biliary tract and liver, he would probably not have developed a malignancy. That a damaged liver, and especially cirrhosis of the liver, can commonly be the precursor of malignant change is a well known fact.

The genesis of the cirrhosis in this case is in accord with the long list of agents and diseases which are known to cause cirrhotic livers and later cancer. This includes chronic biliary disease and biliary obstruction, amebiasis, intrahepatic lithiasis, helminthic infestations, syphilis, hemochromatosis, and various ingested toxins including alcohol. According to Berman [7] who reported 25 cases of primary carcinoma of the liver all of whom had a coexistent cirrhosis of the liver, there may be a racial and sexual susceptibility to hepatic malignancy. His cases were of the Bantu races of South Africa who consume alcoholic beverages from early childhood, but natives of the East Indies and Japan also have an unusually high incidence of carcinoma of the liver. Vint,[8] in analyzing malignant disease in the natives of Kenya, found that 13 per cent of epithelial tumors were primary liver carcinomata which were more common than carcinoma of all other organs including the stomach.

The mechanism by which hepatic cirrhosis causes hepatic cancer is not known, but chronic irritation of the liver tissue is thought to produce cellular proliferation and hyperplasia which may be the precursor of cancer.[9] Berman states that adenomatous hepatic tissue arises in an attempt to compensate for destroyed liver parenchyma. Later the adenomata may undergo malignant degeneration. Steiner [10] attempted to determine the incidence of carcinogenic factor in normal and abnormal (cirrhotic) livers in white people and negroes by injecting extracts of these livers into susceptible animals. All showed about the same incidence of carcinogenic factor for these animals by this method.

The difficulty in diagnosis of this case is apparent from the protocol. Though at first a diagnosis of hypertrophic biliary cirrhosis seemed to fit the clinical picture best, on readmission because of a rapidly growing mass on the anterior surface of the liver, malignancy was suspected, possibly primary locally. In view of the rapid onset and progression of the respiratory symptoms and the pulmonary findings, it was thought that the patient had contracted an extensive pneumonia secondary to his debilitated condition. The fact that supportive therapy including sulfadiazine in adequate amounts and oxygen had no effect whatsoever upon the pulmonary symptoms and signs did not alter this diagnosis. At autopsy the massive infiltration of both lungs with tumor tissue and the lack of pneumonitis were striking. Such a metastatic spread must have appeared with great speed and was probably the immediate cause of death.

The prognosis of congenital cystic dilatation of the common bile duct without operation (anastomosis of the cystic common duct to the duodenum) is usually bad. If early clinical recognition of the disease and proper surgical treatment were carried out, undoubtedly the secondary hepatic changes and in this case neoplastic degeneration could have been delayed or prevented. McWhorter's [11] case lived 13 years in relatively good health after such treatment was carried out.

Summary

1. A case of congenital dilatation of the common bile duct with associated primary hepatic malignancy is presented with autopsy observations.

2. The difficulty in diagnosis is emphasized as is also the importance of clinical recognition and proper surgical treatment early in the course of the disease.

3. The likelihood that the biliary obstruction by the choledochus cyst in this case was the precursor of the malignancy is discussed.

BIBLIOGRAPHY

1. ZINNINGER, M. M., and CASH, J. R.: Congenital cystic dilatation of the common bile duct. Report of a case and review of the literature, Arch. Surg., 1932, xxiv, 77–105.
2. SHALLOW, T. A., EGER, S. A., and WAGNER, F. B.: Congenital cystic dilatation of the common bile duct, Ann. Surg., 1943, cxvii, 355–381.
3. YOTUYANAGI (quoted by SHALLOW, EGER, and WAGNER): Contribution of the etiology and pathogeny of idiopathic cystic dilatation of the common bile duct, Gann., 1936, xxx, 601.
4. WALTERS, W., and SNELL, A.: Diseases of the gall bladder and bile ducts, 1940, W. B. Saunders Co., Philadelphia and London.
5. GROSS, R. E.: Idiopathic dilatation of the common bile duct in children, Jr. Pediat., 1933, iii, 730–755.
6. EWING, J.: Neoplastic diseases. A treatise on tumors, 4th Edition, 1940, W. B. Saunders Co., Philadelphia and London.
7. BERMAN, C.: The etiology of primary carcinoma of the liver with special reference to the Bantu races of South Africa, South African Jr. Med. Sci., 1941, vi, 145–156.
8. VINT, F. W.: Malignant disease in the natives of Kenya, Lancet, 1935, ii, 628–630.
9. BOSE, A. C.: Hepatoma (primary liver-celled carcinoma), Indian Med. Gaz., 1942, lxxvii, 401–402.
10. STEINER, P. E.: The incidence of a carcinogenic factor in the livers of cancer, non-cancer, cirrhotic and negro patients, Cancer Research, 1943, iii, 385–395.
11. MCWHORTER, G. L.: Congenital cystic dilatation of the bile and pancreatic ducts, Arch. Surg., 1939, xxxviii, 397–411.

EDITORIAL

PRIMARY ATYPICAL PNEUMONIA

THIS disease syndrome has occurred so frequently during the past few years that its clinical manifestations are generally known and usually recognized, at least in outspoken cases. Not only has it been frequent in the civilian population, but in the armed forces it has been a major problem, from the standpoint of loss of man power apparently more serious than the bacterial pneumonias.

Knowledge as to the etiology of the disease has not kept pace. Failure to demonstrate any bacterial agent led many investigators to suspect that a virus was concerned, and a number of attempts to isolate a virus have been reported. Some of these earlier investigations have already been reviewed in this journal.[1] Such studies have been handicapped by the fact that all the usual laboratory animals thus far tested are completely or relatively insusceptible to the agent. By carrying out serial inoculations, however, in species of animals which seemed to be relatively susceptible, such as the mongoose, the cotton rat and the hamster, several workers succeeded in establishing infections which were caused by some filtrable agent. In some cases the agent was neutralized by serum from human patients convalescent from atypical pneumonia, although not by serum obtained during the acute stage of the disease. All of these experiments are open to grave objections. Of these, the most serious is the possibility that when a series of animals is used, the agent in the sputum may be contaminated or confused with one of the viruses which cause respiratory infections in these animals under natural conditions. Such an infection may be present in an animal in latent form and be activated so as to cause manifest lesions by the manipulations involved in the inoculation. Although attempts were made to exclude such errors, none of these earlier 'viruses' can be regarded as established.

More recently Eaton, Meiklejohn and van Herick[2] have reported the production of pulmonary lesions after primary intranasal inoculation of sputum in cotton rats and hamsters, which, however, could not be reproduced by serial passages. The lesions consisted of scattered areas of consolidation, small or medium in size, which did not cause death of the animal. They also reported establishing the infection in chick embryos by inoculating into the amniotic cavity filtered sputum or unfiltered sterile lung tissue from human cases of primary atypical pneumonia. This was maintained in the embryos by serial inoculation. No definite abnormalities could be observed in these embryos, however, and the presence of the agent could be demon-

[1] Editorial: The etiology of primary atypical pneumonia, Ann. Int. Med., 1944, xx, 145–149.

[2] EATON, M. D., MEIKLEJOHN, G., and VAN HERICK, W.: Studies on the etiology of atypical pneumonia. A filterable agent transmissible to cotton rats, hamsters and chick embryos, Jr. Exper. Med., 1944, lxxix, 649–667.

strated only by intranasal inoculation of hamsters or cotton rats with suspensions of the lungs, trachea and amniotic membranes of infected embryos. This produced consolidations in the lungs identical with those observed in animals inoculated with sputum. The isolation and propagation of the virus in chick embryos removes the risk of contamination with other viruses while the agent is being passed through a series of animals, but it does not eliminate the possibility of activating some latent respiratory virus in the (single) test animal.

In the case of hamsters, which proved to be the more susceptible species, difficulty at first was often encountered because of the presence of a virus, the 'pneumonia virus of hamsters,' antigenically related to the pneumonia virus of mice. This they apparently eliminated by a preliminary immunization of the hamsters with their own virus, which protected them effectively from this but caused no evident change in susceptibility to the agent of primary atypical pneumonia.

Another obvious objection is that in many animals the lesions are not so conspicuous or distinctive as is to be desired.

That these lesions were not due to some latent respiratory virus was shown, they thought, by the fact that of 970 animals inoculated with infected tissues, 59 per cent showed pulmonary lesions, whereas these were recorded in only 2.24 per cent of 357 controls receiving similar uninfected material.[3] Assuming that the observations were accurately and impartially recorded, the chance that this is a coincidence is very small.

The agent was relatively labile. It could be kept active for long periods if preserved in sealed glass tubes at — 70° C. At ordinary temperatures it rapidly became inert. It was filtrable through collodion membranes of pore diameters which suggested a size of about 180 to 250 mμ.

As further evidence of the etiologic significance of the agent, they report experiments showing that it is neutralized by the serum of patients convalescent from atypical pneumonia.[4] Of 69 cases in which serum was obtained both during the acute stage and in convalescence, 61 per cent showed a fourfold or greater (up to sixty-fourfold) increase in titer of neutralizing antibodies. Either no neutralizing power or no increase in titer was demonstrable in the serum of 15 cases convalescent from pneumonia caused by other agents (nine by influenza A, six by bacteria, eight by viruses of the psittacosis group). The serum from convalescent cases of atypical pneumonia showed no protective power (or no increase in titer) for the viruses naturally occurring in these animals.

Further evidence that primary atypical pneumonia is caused by a virus (in the sense of a filter-passing pathogenic agent which is capable of multi-

[3] EATON, M. D., MEIKLEJOHN, G., VAN HERICK, W., and COREY, M.: Studies on the etiology of primary atypical pneumonia. II. Properties of the virus isolated and propagated in chick embryos, Jr. Exper. Med., 1945, lxxxii, 317–328.

[4] EATON, M. D., VAN HERICK, W., and MEIKLEJOHN, G.: Studies on the etiology of primary atypical pneumonia. III. Specific neutralization of the virus by human serum, Jr. Exper. Med., 1945, lxxxii, 329–342.

plication) is furnished by experiments with human volunteers carried out by the Commission on Acute Respiratory Diseases of the U. S. Army.[5, 6] In the first series, 12 volunteers were inoculated with pooled unfiltered sputum and throat washings from several characteristic cases of primary atypical pneumonia. Of these, 10 developed symptoms of respiratory infection after about a week, of which three showed characteristic symptoms of primary atypical pneumonia of moderate severity with roentgenographic changes in the lungs. The others showed only a mild illness. In a second series, sputum and throat washings from six of these men experimentally infected were employed in a group of 42 volunteers. Of 12 who received unfiltered material, three developed the typical disease and five showed minor respiratory illness. Of 12 who received filtered material, again three suffered a typical attack of the disease and five a minor respiratory illness. Of 18 who received autoclaved material, only one showed evidence of a minor respiratory infection.

The occurrence of mild respiratory infections in these groups of inoculated volunteers in association with cases having demonstrable pneumonia lends support to the view expressed by a number of previous observers that pneumonia is only an occasional manifestation of infection with this agent. It seems probable that in many, perhaps a substantial majority of the cases, it causes only an infection of the upper respiratory passages or a bronchitis which clinically can not be distinguished with any certainty from ordinary 'influenza' or the common cold.

Further evidence supporting this view is found in a report by Breslow [7] of an epidemic of a respiratory infection occurring in a grade school in a small town in Minnesota. Of 186 children in the school, 117 contracted the infection during a two month period. In addition, 74 other cases occurred in the town, 41 of which were secondary cases in members of the households of the infected children. A large majority of the cases had mild infections and received no medical treatment. The relatively small number of severer cases closely resembled atypical pneumonia in its milder form as described by other observers. In five of seven of the severer cases examined, evidence of pneumonia was found in roentgenograms of the chest.

Influenza and ornithosis (psittacosis) were excluded by serological tests. Sera from seven of the severer cases were then submitted to Eaton who tested their power to neutralize the virus he had isolated from cases of primary atypical pneumonia.[4] In five cases the titer of neutralizing antibodies in the convalescent serum was four times (or more) greater than in the serum during the acute stage; in one it showed a two-fold increase, and in one both specimens showed a high titer. It seems, therefore, that the agent

[5] Commission on Acute Respiratory Diseases: An experimental attempt to transmit primary atypical pneumonia in human volunteers, Jr. Clin. Invest., 1945, xxiv, 175–188.

[6] Ibid.: Transmission of primary atypical pneumonia to human volunteers, Jr. Am. Med. Assoc., 1945, cxxvii, 146–149.

[7] Breslow, L.: Epidemic of acute respiratory disease associated with atypical pneumonia, Jr. Clin. Invest., 1945, xxiv, 775–779.

concerned in these cases was serologically identical with the virus isolated by Eaton et al. Unfortunately none of the milder cases was tested in this way, but the epidemiological evidence strongly suggests that many of them, at least, were caused by the same agent.

Although the evidence reviewed is not entirely conclusive, this work strongly suggests that a substantial proportion of the cases of primary atypical pneumonia are caused by a specific virus which appears to be different from any previously reported. It is quite possible that other cases, clinically similar, may be caused by viruses which are antigenically different, as has been shown in the case of influenza. It is also highly probable that the infection produced by this agent may vary from a mild disease resembling a common cold to a severe illness with extensive pulmonary lesions. It is manifestly one of the most important of the common respiratory infections.

REVIEWS

The Specificity of Serological Reactions. Revised Edition. By KARL LANDSTEINER, M.D. The Rockefeller Institute for Medical Research. 310 pages; 21.5 × 14.5 cm. 1945. Harvard University Press, Cambridge, Mass. Price, $5.00.

The text of the revised edition was completed by Dr. Landsteiner before his untimely death in June 1943, and was prepared for publication by E. K. Landsteiner. The book follows the form of the earlier edition but the material has been brought up to date. Owing to the war, recent foreign material, except the British, was not available for review.

Following the introduction which outlines immunological phenomena and gives the general nomenclature, there are two chapters devoted to the serological specificity of proteins and to cell antigens. This is followed by a section on artificially prepared conjugated antigens and the reaction of simple chemical cellular substances is then presented.

The volume concludes with a chapter by Dr. Sinus Pauling entitled "Molecular Structure and Intermolecular Forces."

The book bears the mark of an outstanding investigator and will remain a classic contribution to this field of investigation.

M. A. A.

Textbook of Obstetrics. By HENRICUS J. STANDER, M.D., F.A.C.S. 1287 pages; 25 × 17 cm. 1945. D. Appleton-Century Co., New York. Price, $10.00.

This edition represents the Ninth Edition of "Williams' Obstetrics," the first six of which were written by the late Dr. J. Whitridge Williams. This is the first edition of this work which appears directly under the name of Dr. Stander, who is Professor of Obstetrics and Gynecology in the Cornell University Medical College.

The author of this textbook for students and practitioners states in his preface that the art and science of obstetrics as taught in the Cornell University Medical College and practised in the New York Lying-In Hospital are presented.

The general plan of the work is similar to the previous editions, but the arrangement is different in that the subjects are presented in sections and sub-sections rather than in chapters. The publishers state that the book has been revised, rewritten and reillustrated.

In complying with wartime standards reducing the bulk of paper, a welcome reduction in the size of the book has been accomplished. The type is clear and readable. There are 973 splendid illustrations on 740 figures, many of which are new and many are in color. Ten sections and 49 sub-sections cover the field of obstetrics. Historical and many of the theoretical considerations appear in small type. Although the bibliography at the end of the sections and sub-sections is quite extensive, one could wish that more of the modern references had been included.

The author's style of writing is clear and forceful, but because of the magnitude of the scope, and the multiple references and statistical data appearing in the text, it is the belief of the undersigned that some of the effectiveness as a book primarily for students thereby has been lost.

No mention is made of the various clinical uses of Willett's forceps such as in the treatment of certain types of placenta previa. Insufflation of the vagina is advocated

as a method of treatment of trichomonas vaginalis vaginitis during pregnancy, but the possible dangers of such a mode of treatment during pregnancy are not pointed out. No reference is made to the use of the newer anti-malarial drugs in the treatment of malaria during pregnancy.

Despite these factors, this textbook is a complete and modern presentation of the conservative practise of obstetrics in the New York Lying-In Hospital, and undoubtedly will remain among the classics in its field.

J. E. S.

Penicillin in the Treatment of Infections. By CHESTER S. KEEFER, M.D. and DONALD G. ANDERSON, M.D. 48 pages; 15 × 18 cm. 1945. Oxford University Press, New York.

In view of the rapid advances being made in chemotherapy, especially in the use of antibiotics, it is impossible for any one monograph to keep abreast of the developments in the field. However, this concise yet inclusive volume presents in a well-organized discussion the information necessary for the intelligent clinical use of penicillin.

The history, characteristics and pharmacology of the substance are considered briefly, followed by a more detailed discussion of its clinical uses in the more common infections. The toxic reactions are included in an interesting presentation and a bibliography containing 109 references emphasizes the intense study that has been under way in this field.

The data here accumulated confirm the authors' statement in the final paragraph that penicillin "is without doubt the most effective agent for the treatment of infectious diseases ever discovered."

J. Z. B.

BOOKS RECEIVED

Books received during February are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

An Introduction to Essential Hypertension. By RICHARD F. HERNDON, M.D., F.A.C.P. 88 pages; 23 × 14.5 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, $2.50.

Dr. W. C. Roentgen. By OTTO GLASSER, Cleveland Clinic Foundation. 169 pages; 22 × 14.5 cm. 1945. Charles C. Thomas, Springfield, Ill.

Roentgen Diagnosis of Diseases of the Gastrointestinal Tract. By JOHN T. FARREL, JR., M.D., Clinical Professor of Radiology, Graduate School of Medicine, University of Pennsylvania. 271 pages; 23.5 × 15.5 cm. 1946. Charles C. Thomas, Springfield, Ill. Price, $5.50.

Preventive Medicine and Public Health. By WILSON G. SMILLIE, A.B., M.D., D.P.H., Sc.D. (Hon.). 607 pages; 22 × 14.5 cm. 1946. The Macmillan Company, New York. Price, $6.00.

Digitalis and Other Cardiotonic Drugs. By ELI RODIN MOVITT, M.D. 204 pages; 24.5 × 16 cm. 1946. Oxford University Press, New York.

Neurosyphilis. By H. HOUSTON MERRITT, A.B., M.A., M.D., RAYMOND D. ADAMS, M.A., M.D., and HARRY C. SOLOMON, B.S., M.D. 443 pages; 24 × 16 cm. 1946. Oxford University Press, New York.

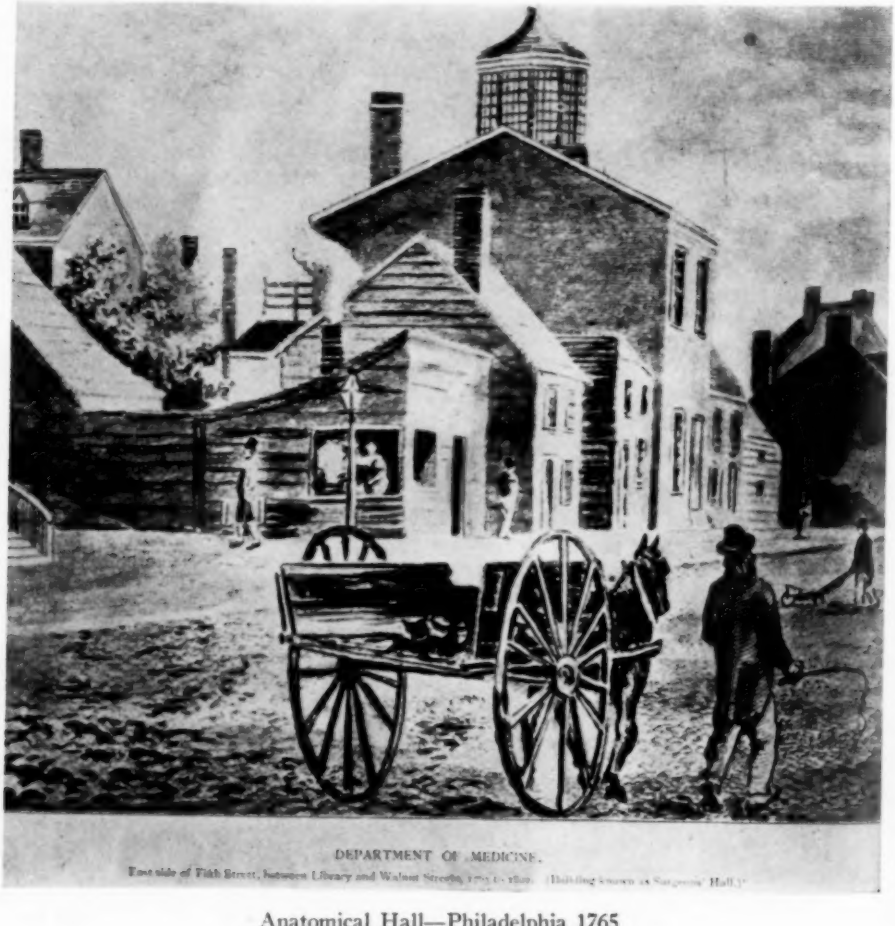
Science and Scientists in the Netherlands Indies. Edited by PIETER HONIG, Ph.D., and FRANS VERDOORN, Ph.D. 491 pages; 27 × 18 cm. 1945. Board for the Netherlands Indies, Surinam and Curacao, New York City. Price, $4.00.

Convulsive Disorders. Edited by RUCKER CLEVELAND, Ph.D. 83 pages; 25.5 × 18 cm. 1945. Research Laboratories and The Department of Clinical Investigation of Parke, Davis and Company.

PHILADELPHIA AND AMERICAN MEDICINE

THE approaching twenty-seventh Annual Session of the American College of Physicians, to be held in Philadelphia, May 13–17, 1946, will bring the members of this College back to the cradle of organized medicine in this country. If a cradle were all that the city of Philadelphia had to offer the visiting physician, it is obvious that the meetings would, in all probability, have been scheduled elsewhere. The truth is, that today Philadelphia's physicians welcome their colleagues not to a city of the past, but to one into which the destiny which broods over cities has breathed a timeless and unquestioned devotion—that towards the art of medicine.

Philadelphia, in size the third city of the country, vies with Chicago for first place in the number of recognized medical schools, each having five.



Anatomical Hall—Philadelphia 1765
Cradle of American Medical Education.

The statistics on hospitals and physicians in the three cities are approximately in proportion to their population.

The Medical School of the University of Pennsylvania * in September of this year will undertake for the one hundred and eighty-first year to offer organized medical instruction to the youth of this and other lands. The record is unique in this country. This first medical school in the colonies came into being in 1765 as the Department of Medicine of the College of Philadelphia, largely through the efforts of a distinguished Philadelphia physician, John Morgan, who, appropriately, was elected to the first medical professorship in the colonies. Morgan belonged to that great group of Philadelphia physicians whose superb vigor of mind and body, and whose devotion to the progress of American medicine, left their impress indelibly upon the face and in the soul of the city.

On June 21, 1768, ten students walked out of the commencement exercises of the College of Philadelphia (now the University of Pennsylvania), with the first medical degrees granted by the first medical school in the country. Since that day, approximately 18,000 other youths have followed in their footsteps.

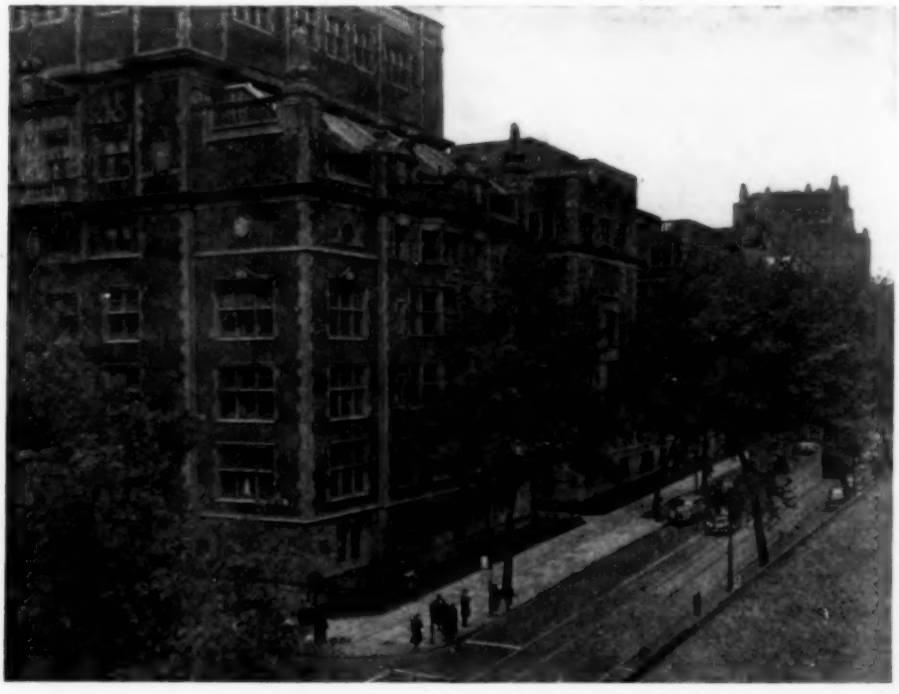
The buildings that have housed the Medical School have been several; the catalogue of professors is long and illustrious. Over the earlier homes it would not be profitable at this time to pause. From the list of professors, piety and affection demand that we single out at least the names of William Shippen, Jr., Benjamin Rush, James Woodhouse, Benjamin Smith Barton, Caspar Wistar, Nathaniel Chapman, Philip Syng Physick, William P. Dewees, William Edmonds Horner, Robert Hare, George B. Wood, Hugh Lenox Hodge, Joseph Leidy, D. Hayes Agnew, William Goodell, William Pepper, Alfred Stille, William Osler, Richard A. F. Penrose, H. C. Wood, Leonard Pearson, C. L. Leonard, John Ashhurst, George W. Norris, Louis Duhring, J. William White, George A. Piersol, E. T. Reichert, John Marshall, James Tyson, John H. Musser, John G. Clark, Edward Martin, Alfred Stengel, Barton C. Hirst, John B. Deaver, George E. de Schweinitz, Charles K. Mills, William G. Spiller and Charles H. Frazier.

In 1873 the University moved to its present location in West Philadelphia adjoining the grounds of the Philadelphia General Hospital. The University Hospital was erected on the campus at that time. The Laboratory of Hygiene was built in 1892, and the Laboratories of Pathology, Physiology, and Pharmacology were formally opened in 1904. In 1928, however, there was attached to their building a splendid five-story structure which now houses the Departments of Anatomy, Physiological Chemistry, Research Surgery, and the Anatomy Department of the Graduate School of Medicine.

In the same year, work was begun on the Maloney Pavilion. This ten-story building at Thirty-Sixth and Spruce Streets connects with the Hospital

* The following material has been assembled and in large part taken verbatim from the Reports and Announcements and from individual histories of the various institutions.

and furnishes quarters for the William Pepper Laboratory of Clinical Medicine (originally this laboratory occupied a building erected for it in 1894, the first unit of its kind in the country), the John H. Musser Department of Research Medicine, the Eldridge R. Johnson Foundation for Medical Physics, the Department of Physical Medicine and the George S. Cox Medical Research Institute, various special diagnostic clinics of the Medical Out-Patient Department, and about 25 private rooms.



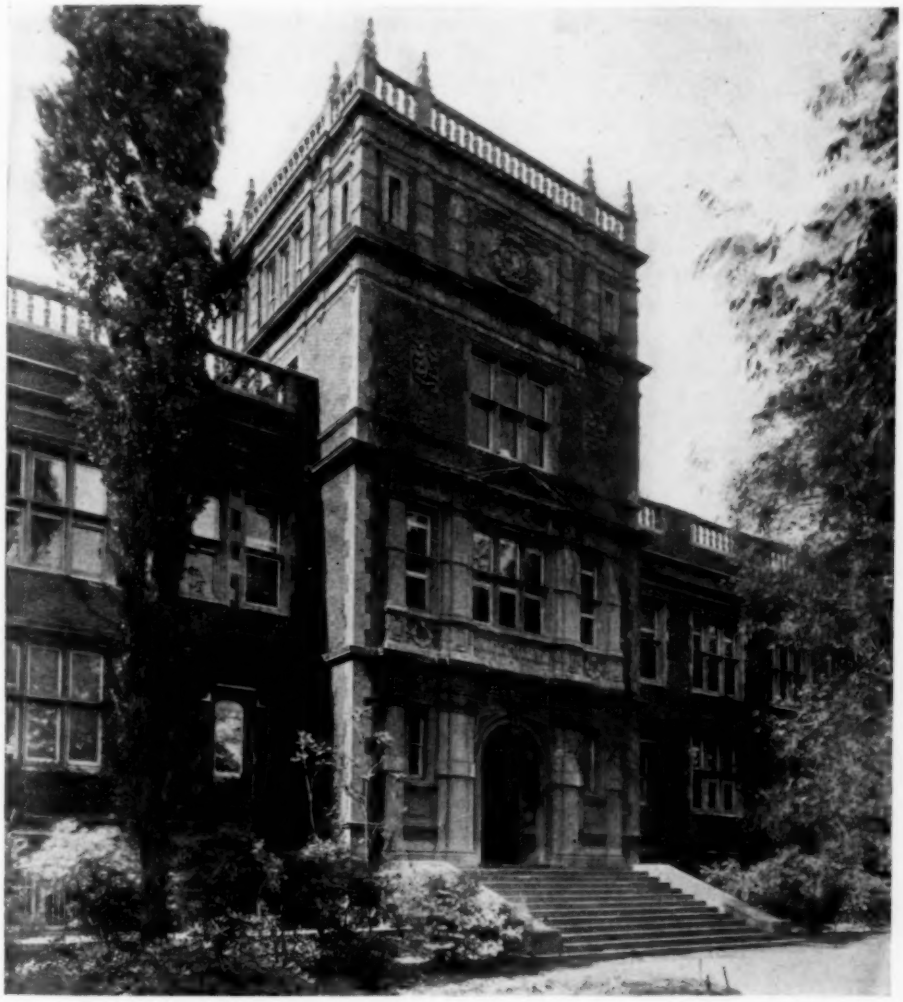
Hospital of the University of Pennsylvania.

The Wistar Institute of Anatomy and Biology, at Thirty-Sixth Street and Woodland Avenue, incorporated in 1892, was the first American University Institute devoted to advanced study and research in anatomy and biology. The Henry Phipps Institute for the study, treatment, and prevention of tuberculosis, at Seventh and Lombard Streets, was established in 1903, the first fully organized and equipped institution of the kind with University connection.

Other notable "firsts" of which the School of Medicine is entitled to boast include the graduate courses in public health leading to the degree of Doctor of Public Health; a separate building for research in, and the teaching of, hygiene; the Department of Research Medicine whose members devote practically their entire time to investigation.

The School includes in addition to the Research Foundations mentioned above, the Robinette Foundation, the Gynecean Hospital Institute of Gynecologic Research, and the Laboratory of Dermatological Research.

The University Hospital, which is an integral part of the School, and whose staff is drawn entirely from members of the medical faculty, was the



Main Entrance to Medical Laboratories, University of Pennsylvania.

first in the country to be built by a university for the use of its medical school. Several years ago the Neurologic Institute of the Philadelphia Orthopaedic Hospital and Infirmary for Nervous Diseases was merged with the University Hospital and housed in a four-story building on the hospital grounds. There are at present available a total of 729 beds. During the

fiscal year of 1944 to 1945, there were 16,073 hospital admissions, 115,399 visits to the out-patient departments, and 11,383 surgical operations were performed. Students of all four classes are taught here every clinical subject.

This medical school, in brief, in the course of 181 years of active life has met with amazing resource and courage the demands of our increasingly complex civilization, so that today its equipment enables it to offer its students every advantage of theoretical, practical, and research study. Age has indeed not withered, nor custom been allowed to stale.

Graduate Hospital of the University of Pennsylvania.

The University's Graduate School of Medicine, located at Nineteenth and Lombard Streets, was organized in 1916 by a merger between the University and the old Medico-Chirurgical College of Philadelphia, which had

been founded in 1881. In 1918 the Philadelphia Polyclinic and College for Graduates in Medicine merged with the Graduate School of Medicine and formed the Polyclinic Section. Later additions of assets included the Diagnostic and Howard Hospitals, and the North American Sanitarium.

The Graduate School of Medicine today is, administratively, a separate university unit, or association of units, operating in complete coöperation with the School of Medicine, and, like the latter, is administered ultimately by the University's vice-president in charge of medical affairs and its Board of Trustees. The students of the Graduate School are suitably qualified physicians who after a basic year of formal systematic training may become, substantially, clinical or research assistants to members of the faculty throughout the city, intramurally and extramurally, or to carefully selected physicians in other communities. The essential feature of the Graduate School's "Pennsylvania Plan" of graduate medical education is the upbuilding of an extensive coöperation between the central organization, that is, the Graduate School, and extramural medical organizations and their staffs. At present, 50 of Philadelphia's medical organizations are found to be thus coöperating. The Graduate Hospital, covering more than one city block, with a capacity of 461 beds, is the clinical teaching center of the school. During the year 1944–45, its activity rate was 68,861 bed days, 4,128 operative cases, and 79,004 out-patient visits. The Graduate School of Medicine of the University of Pennsylvania is today the only institution of its kind in Philadelphia.

Jefferson College and Hospital. Philadelphia's second medical college, in point of time, is an equally vigorous ancient of the second generation. This is the Jefferson Medical College, founded in 1825, as the Medical Department of the Jefferson College of Canonsburg, Pennsylvania. Its first class was graduated in the following year. In the intervening 120 years, it has conferred a medical degree upon approximately 17,500 of its students.

The College today occupies a handsome building on Walnut Street, just west of the old College building at Tenth and Walnut Streets where now is situated its Curtis Clinic. The College building, opened in 1929, represents, like the Maloney Pavilion of the University of Pennsylvania, a thoroughly modern response to the technical developments of the day as they affect the equipment for medical instruction and research. Herein are contained, in addition to administrative offices, professors' rooms, work rooms, recitation, lecture, demonstration, and assembly rooms, laboratories large and small, for the use of the various departments, a library, and the College Museum. More recently an additional floor in the College Building has been completed as a fully equipped modern Department of Pharmacology. At present an entire floor is under completion for offices and research laboratories for the Departments of Experimental Medicine, Experimental Surgery, Neuropathology and Neurosurgery. In 1941, the Cardeza Foundation for Research on Diseases of the Blood and Allied Conditions was organized. This Foundation now operates the Transfusion-Plasma

Jefferson Hospital.

Unit, Photographic Biologic Laboratory and Research Laboratories of the Staff. A modern air-conditioned animal house and operating rooms have also been completed.

The clinical teaching is today carried on largely in the College's Hospital, adjacent to the College itself. This building, opened in 1907, has a capacity of 475 ward beds, in addition to 272 for private and semi-private patients, and offers every facility for this purpose. Under the supervision of professors and experienced instructors, students are required to participate in operations and to assist in the administration of anesthetics. When the interests of the patient are not thereby jeopardized, the student may follow the case from admission to discharge.

The Curtis Clinic, adjoining the College, and conforming to it architecturally, is the out-patient unit. The building is planned so as to group the various medical, surgical, and specialty divisions. The Hospital's central location insures an exceptionally large service demand, particularly in the out-patient department. The surgical division of the Jefferson Hospital performed 8,593 operations in the year ending May 31, 1945. For the same period there were 63,062 admissions to the various departments of the Hospital and the total out-patient service amounted to 195,697 visits.

In 1924, the Samuel Gustine Thompson Annex to the Jefferson Hospital was opened. This building contains the teaching clinical amphitheater, seating 550, a maternity department, bronchoscopic wards, and a teaching clinical laboratory upon the roof. The Department of Anatomy, including Descriptive and Practical Anatomy, Histology and Embryology, and Anatomy as applied to Medicine and Surgery, is housed in a building of its own at Clinton and Eleventh Streets, a few blocks from the College. This is the Daniel Baugh Institute of Anatomy, containing laboratories, a museum, amphitheaters, and a notable departmental anatomical reference library. The Department for Diseases of the Chest is likewise set apart, in a building at 238 Pine Street. Although the activities here are concerned largely with the problem of tuberculosis, other related conditions are studied and treated. Twelve students are selected from the fourth year class to reside in the department and assist in the preparation of histories and in the special study of patients.

Jefferson's faculties, which weathered severe storms in the early days, have contained some of the most distinguished Philadelphia physicians of national reputation: such men, for instance, as George McClellan, John Eberle, Daniel Drake, Nathan R. Smith, Robley Dunglison, Joseph Pancoast, J. K. Mitchell, Thomas D. Mütter, Charles D. Meigs, Franklin Bache, Samuel D. Gross, Samuel H. Dickson, Robert E. Rogers, the younger Gross, J. M. DaCosta, Roberts Bartholow, W. W. Keen, Hobart Amory Hare, James Wilson, Edward P. Davis, and J. C. DaCosta. The College's history is a colorful one, and its achievements loom large in the history of the city's and the nation's medical life.

Hahnemann Medical College and Hospital. In 1845, homeopathy had practitioners (about 250 in number) in 22 states, but no institution where homeopathy was taught. Its doctrine, in fact, was promulgated under a cloud of disapproval by the medical profession, which culminated in resolutions passed, in 1847, by the newly formed American Medical Association, tending to stigmatize it as irregular. It was in an attempt to gain legal recognition for the system that the Homeopathic Medical College of Pennsylvania, the oldest of its kind in the world, was founded in 1848. In 1869, this college was consolidated with the Hahnemann Medical College of Philadelphia under the corporate name of the Hahnemann Medical College of Philadelphia, and in 1885 the corporation of the Hahnemann Medical College and Hospital of Philadelphia was brought by merger into existence and located at its present site.

With admirable sincerity of purpose the College has pursued its course, constantly strengthening its base and widening its curriculum in line with the developments in the fields of medicine. Its requirements today include two years of college work as a minimum, preference being given those applicants with more preparation. The Medical School offers a standard four years' course, and confers upon its graduates, by provision of its state charter, two degrees, those of Doctor of Medicine and Doctor of Homeopathic Medicine. Although special attention is given to Materia Medica and Therapeutics and to the principles of Hahnemann, Hering, Dunham, and other noted men in the field, the prime object of the school is to give a broad and thorough medical education. This it successfully achieves.

The College building contains lecture rooms, a large library and museum, laboratories, rooms for operative surgery and practical obstetrics, the administrative and faculty offices and reading rooms. The College Library may be divided into two departments. One contains about 15,000 volumes and is especially of historical interest. Here are found Dr. Hering's notable collection of the writings of Paracelsus, Dr. A. R. Thomas' collection of very old and rare anatomical books, all of Hahnemann's works in the original and the most complete library of homeopathic literature in existence. The other constitutes a valuable working library and reading room for students and contains a file of the principal medical and scientific journals. Investigation in medical literature is considered an essential part of the college course.

The new Hahnemann Hospital, 20 floors in height, was opened in 1928 and has a total capacity of 700 beds, 370 of which are public. Over 12,000 bed patients are treated in a year, and an average of over 125,000 visits are made to the out-patient department. The Hospital is equipped with electrocardiographic, fluoroscopic, basal metabolism and clinical laboratories. The arrangements are such that the operating units are coördinated on the same floor with the roentgenological department, the clinical and pathological laboratories of the Hospital being on the floor directly below. As

with the other schools and hospitals which we have mentioned, the faculty of the School and the staff of the Hospital are one, and the clinical material presented by the Hospital is directly available for teaching purposes and is used constantly.

Hahnemann Medical College and Hospital.

The tendency of the day in this country is unquestionably toward greater uniformity in medical instruction, and to the advance along this line Hahnemann College has devoted itself with obvious success.

Jewish Hospital.

Woman's Medical College of Pennsylvania. The position of women in American medicine would probably be as uncomfortably anomalous today as it was in the early years of our national life, had there not come quietly into existence in 1850, in Philadelphia, an institution quaintly called, in the terminology of the day, the Female Medical College of Pennsylvania. This was the first college in the world regularly organized for the medical education of women, and it is still the only medical school in the United States exclusively for women.

The opening session of the College found 40 students enrolled for instruction by a faculty of six, all men. The first class graduated numbered eight, of whom one, Dr. Ann Preston, was soon elected to the Chair of Physiology and Hygiene, the first woman to have a place on the faculty. Today, well over two-thirds of the faculty are women.

It was to be expected that the problem of adequate clinical instruction would be a difficult one for the pioneers to overcome, and such indeed it was. In 1860, we find the first official reference to the founding of the Woman's Hospital of Philadelphia. A lack of foresight in the acquisition of its charter, however, led to a situation in which the College and the Hospital came under the management of dual groups, which hindered the use of the Hospital for clinical teaching. Fortunately, other clinical opportunities were opening up. On January 2, 1869, the distinguished Alfred Stille prefaced his lectures in the amphitheater of the Philadelphia Hospital with these words:

"Ladies and Gentlemen: I have pleasure in meeting you today. It is the first time in my medical experience that I have had the opportunity of

addressing women among the audience of my pupils. We are sometimes shocked at what is novel, simply because it gives us an unaccustomed impression, but in the present instance I must say that, so far as I am personally concerned, I not only have no objection to seeing ladies among a medical audience, but, on the other hand, I welcome them."

In 1869, likewise, the Board of Managers of the Pennsylvania Hospital came nobly to the rescue with an invitation to the women students to attend the clinical lectures at that institution. On November 6 of that year about 30 women students accepted the invitation, but presumably somewhat to their chagrin. The novelty was not only a shock to the male students of the Pennsylvania Hospital, but it was received with conduct on their part which quickly made of the incident a *cause célèbre*. The way of the pioneer, which is, in a sense, that of the transgressor, was ever hard.

Woman's Medical College.

The site and buildings of the present College and Hospital, opened in 1930 and occupying approximately 10 acres, present the former Female College of Pennsylvania, under its present title, as one of Philadelphia's distinguished medical institutions. The Hospital, containing 152 beds and 21 bassinets, is conducted by the Corporation under the professional direction of the faculty. A fully equipped heart clinic was opened in 1932 and a bronchoscopic clinic in 1933 to 1934. An out-patient clinic is conducted at Barton Dispensary, 1309 North Twenty-Second Street, as well as at the Hospital. The students today enjoy the extramural privileges, such as the use of the Libraries of the College of Physicians and the Academy of Natural Sciences, and of various clinics, accorded their male colleagues. Much of their clinical teaching is now conducted in the wards and clinics of the Philadelphia General Hospital, the Woman's Hospital, the Memorial Hos-

pital at Roxborough, the Pennsylvania Hospital and its Institute for Nervous Diseases, St. Christopher's Hospital, and the Philadelphia Hospital for Contagious Diseases. If the millennium has not yet been attained, that is a circumstance of which we are all, men as well as women, in one way or another the victims. Certainly, the work of the Woman's Medical College of Pennsylvania has contributed not a little toward defining the road forward.

Temple University School of Medicine. The Medical Department of Temple University was opened in 1901. It is, therefore, the youngest of Philadelphia's five recognized medical schools. No one, however, with even a bowing acquaintance with the country's medical schools will be deceived by that fact. Its status today as one of our major schools of medicine is uncontested. This position it has achieved in comparatively few years through its success in drawing to it a distinguished faculty and in furnishing them and their students with the most modern equipment for research and instruction. Its success in attracting medical students may be gauged by the fact that, though the first-year class is limited to 100, well over 2,000 applicants are considered annually by the Committee on Admissions.

If the annals of this school are as yet too brief to provide a historian's field-day, it should at least be pointed out that the Temple University School of Medicine was the first coeducational medical school to be established

Temple University Medical School and Hospital.

in Pennsylvania. Its third graduating class, in fact, included two women. Thus far at least had we traveled since the embattled days of '69.

The present building occupied by the School was opened in 1930. It is situated on Broad and Ontario Streets, directly opposite the University's Hospital. Dispensaries and administrative offices share with the library the first and second floors. The various departments are housed in the third to sixth floors, while the seventh contains medical and research rooms and storage facilities for mammals, rodents, etc.

The Temple University Hospital, where most of the clinical teaching is done, is directly under the control of the faculty. It ranks with the larger institutions of its kind in the city in facilities and equipment, having a bed capacity of 469, which affords abundant material for every branch of clinical instruction. A laboratory building on the hospital grounds provides a well equipped clinical laboratory, an autopsy room, private laboratories for original research, and rooms for teaching purposes.

Temple University itself, founded in 1884 by Russell H. Conwell, celebrates this year its sixty-second anniversary. The seal of the University bears the motto *Perseverantia vincit*. As one looks at the achievements of its medical school in so short a period as forty-five years, one is almost tempted to believe that perseverance, soon or late, if the object be a fair one, does win.

Philadelphia College of Pharmacy and Science. It would certainly not be fitting to close this brief survey of Philadelphia medical schools without recalling to the visitor's attention the fact that the Philadelphia College of Pharmacy and Science, at Forty-Third and Kingsessing Avenue, today one of the leading institutions of its kind in the country, was also the first college of pharmacy in the new world. The history of this college, founded in 1821, in Carpenter's Hall, seat of the Provincial Assembly and of the first general Congress of the Colonies, covers practically the history of pharmaceutical education in this country. Its founding, by 68 druggists and apothecaries bent upon education by the masters of their craft, indicates once more the early and deep devotion of Philadelphia's medical groups to the highest development of their science. And it is by way of illustrating the high quality of instruction which has always been maintained in the College that we recall as members of its faculties George B. Wood, Joseph Carson, Franklin Bache (great-grandson of Benjamin Franklin), Robert Bridges, William Proctor, John M. M. Maisch, Samuel P. Sadtler, and Joseph P. Remington.

Hospitals. The hospitals which are directly connected with the various schools of medicine have already been briefly mentioned. We may be forgiven under the circumstances if from the many others we select for a brief introduction those which will be the most intimately involved in the forthcoming meetings.

The Pennsylvania Hospital. To those who have the fortune to see medicine in its historical perspective, the Pennsylvania Hospital is perhaps more than any other medical institution in the country a rich source of

pleasure. One of the largest and most important hospitals in the city today, it yet retains both in its exterior and in its interior much that is evocative of its long and notable past. It is, in fact, the oldest hospital in the United States which was intended wholly for the sick and wounded and which has continued on its ancient site and maintained its original name.

Pennsylvania Hospital.

The founding of this Hospital was predominantly the work of Benjamin Franklin and his close friend, the physician, Thomas Bond. The latter is remembered today also as the originator of the Bond splint for the treatment of fractures of the forearm, and for the invention also of an instrument for extracting foreign bodies from the esophagus, thus inaugurating what seems to have become an old Philadelphia custom.

The roster of the Hospital has always contained the names of many of the city's leading physicians—the Bonds, Morgan, Shippen, Jones, Rush, Physick, James, Parish, Otto, Ward, Pepper, Gerhard, Agnew, Packard, Ashhurst, Meigs, Harte, Stengel. This gratuitous service was instituted by the Hospital's first physicians. It is estimated that the services performed by the Staff today are worth well over $500,000 a year.

The present divisions of the Pennsylvania Hospital are the Department for the Sick and Injured, the Department for Mental and Nervous Diseases, and the Institute of the Pennsylvania Hospital. The Philadelphia Dispensary, founded in 1786, is now also carried on as part of the "Out-Patient Department of the Pennsylvania Hospital and Philadelphia Dispensary."

The Department for the Sick and Injured, at Eighth between Spruce and Pine Streets, occupies the site it first moved to in 1756. An interesting analysis of its service, given in one of the Hospital's recent Annual Reports, indicates that during the year there was an application for either emergency

or ward care every 14 minutes; a ward bed or a private room received a new patient every 84 minutes; the Out-Patient Department cared for a patient every three and two-fifths minutes; the police patrols brought a patient to the door every five hours and 22 minutes; a surgeon performed an operation every two hours and four minutes. No further words are needed to show that this Department of the Hospital, which, like the Jefferson College Hospital, is in the center of the city, fulfills the extraordinary demands made upon it as courageously as it did in the days when it was a new institution in a New World.

The Department for Mental and Nervous Diseases and the Institute are reminders that the Pennsylvania Hospital from its origin was the pioneer in the Colonies in the treatment of the mentally unstable not as criminals but as patients suffering with mental disease, subject to individual treatment and eventual return to reason. This department was moved to its site in West Philadelphia, at Forty-Fourth and Market Streets, in 1841, and its first Superintendent, Dr. T. S. Kirkbride, so impressed his personality upon the institution that, for many years, it was familiarly known as "Kirkbride's." The treatment of its more than 200 patients is naturally on an individual basis, planned after a comprehensive study of the patient, and employs such methods, depending on the diagnosis, as fever, occupational and physiotherapy, the Aschner treatment, music, recreation, etc.

Institute of the Pennsylvania Hospital.

The Institute, at Forty-Ninth and Market Streets, represents the Hospital's latest development in the line of treating mental conditions. The keynote of its work is that of prevention of mental and nervous illness. Here in quiet and comfortable surroundings the attempt is made to solve the emotional problems as much as possible by natural means under medical direc-

tion. Civic recognition of the work of the Institute was signalized in 1933, by the presentation of the Philadelphia Award to the Chief of Clinical Service and Medical Director of the Institute. The career of the Pennsylvania Hospital has been memorable in many ways, in none other perhaps so memorable as in its steady devotion to the understanding and healing of the mentally sick and injured.

Philadelphia General Hospital. The Philadelphia Almshouse was erected in 1731 or 1732. In 1835, it officially adopted the title "Philadelphia Hospital," which again gave way, in 1902, to the title it bears today, namely, "Philadelphia General Hospital."

The history of this institution from its earliest days as an alms—or "bettering" house, receiving, in the older fashion, the poor, the sick, and the lunatic, to its position today as the largest hospital in the city and one of the largest in the country, forms one of the more remarkable chapters in the history of medicine in Philadelphia.

Though the title "Philadelphia Hospital" was not adopted until 1835, there is ample evidence that a hospital department existed at the Almshouse from its early days. And the title adopted in 1835 was again curiously inconclusive in that the Almshouse and the Hospital continued to be located together at the present site of the Philadelphia General Hospital until 1920, when the Almshouse was removed to separate quarters away from the hospital grounds.

The earliest records of the Hospital, unfortunately not so well preserved as those of the Pennsylvania Hospital, show that the pre-Revolutionary attending physicians numbered many of the famous group so intimately connected with the founding and the early days of the Pennsylvania Hospital and the Medical School of the present University of Pennsylvania. Since those days the staff of the Hospital has included at one time or another Philip Syng Physick, Caspar Wistar, Benjamin Smith Barton, Nathaniel Chapman, T. C. James, Hugh Lenox Hodge, S. D. Gross, D. Hayes Agnew, William Osler (whose notable postmortem work was done here), S. Weir Mitchell, J. H. Musser, H. C. Wood, Louis A. Duhring, W. W. Gerhard (it was in this Hospital that he made his clinical observations on the differentiation of typhus from typhoid fever), Alfred Stengel, William Hughes, Joseph Sailer, David Riesman, DeForest Willard, and others of equal prominence.

When the Hospital moved, in 1834, to its present site and thereafter assumed the name "Philadelphia Hospital," it assumed unofficially the name "Blockley," from the township in which it was placed, and this was the name by which it was commonly known, to which it still occasionally answers today. In 1834, it was supposed to accommodate 400 sick, 200 more, if necessary, and was difficult of access from the medical schools. Today it has a capacity of about 3,000 beds and has as its near neighbor the Medical School of the University of Pennsylvania.

The greatest strides in the new Philadelphia General Hospital have been

taken in the last 15 years. This period has seen the development of the outpatient clinics to which well over 60,000 visits are paid each year. Particularly noteworthy is the work being done in cardiology, in metabolism, in occupational diseases, in tuberculosis, in radiology, and in the neuropsychiatric, prenatal, and postnatal clinics. The Saturday morning clinics, for

Philadelphia General Hospital.

the general practitioners of the city, are a prominent feature of the Hospital's life today. Cases of special interest in the Hospital are drawn upon for material and some prominent physician, not necessarily of the staff, is invited to talk upon them.

This period has seen, also, the erection of a building for the adequate housing of the interns and resident physicians, and one for the care of the female tuberculous. The impressive proportions of the Philadelphia General Hospital today, an idea of which can be readily gained from the accompanying aerial view, and the notable work which it continues to do, are further tributes to the vigor and integrity of Philadelphia's medical men who have had occasionally, in making this Hospital possible, severe political battles to wage in order to maintain adequate scientific independence and progress.

The Children's Hospital. The Children's Hospital of Philadelphia, at Eighteenth and Bainbridge Streets, in the past year opened another wing (Rush) of its projected final group. This well emphasizes the continuing growth of the country's oldest hospital designed exclusively for children, established in 1855, and the third such hospital in the world. The first home of the Hospital had accommodation for 12 patients; the present Hospital, opened in 1916, has a capacity of 156 beds.

The primary purpose of the Hospital was to care for children suffering from diseases which could not be properly treated in their homes. An interesting commentary on the changes of direction which the progress of medicine takes is the Hospital's Department for Prevention of Disease, inaugurated in 1914, as an outgrowth of a previous Social Service Department. This Department, the first of its kind in any hospital in America

Children's Hospital.

and one which draws visitors from all over the world, treats annually both in their homes and in the clinics well over 100,000 patients. This, in addition to an annual regular out-patient service of over 40,000 visits and an in-patient roll of approximately 3000 patients, is sufficient evidence of the remarkable service which this Hospital gives to the children of Philadelphia. As a further development in the general field of Child Welfare, the Hospital established in 1923, a Child Guidance clinic. This clinic was designed to examine and recommend the right management of problem children, truants, potential criminals, and other misfits. It has under its guidance constantly over 800 of these children. Philadelphia, once again, has proved itself a pioneer in the now accepted doctrine, proposed so early in our medical history by the Pennsylvania Hospital, that the physician cannot exclude from his realm the unsound mind, no matter how sound the body.

Lankenau Hospital. The Lankenau Hospital, incorporated in 1860, opened for patients in 1866, as the German Hospital of the City of Philadelphia. Its present name honors its second President, John D. Lankenau, whose personal care and generosity are credited with being the chief agents through which it reached its present standing among the city's hospitals.

Originally designed as a hospital in which the German people of Philadelphia might be treated by physicians and nurses who could speak their native tongue, the Hospital has inevitably come to serve a wider function. Though the Hospital is excellently equipped for its annual in-patient service demand of about 4000 patients and an out-patient visit total of about 37,000, probably its chief interesting feature is its Research Institute. This was built in 1925, by the late Rodman Wanamaker, at the cost of about half a million dollars. The activities of the Clinical Laboratories of this Research Institute include in a year about 60,000 examinations of all types. A Division of Art and Photography records the completion of numerous drawings, photographs, and photomicrographs of patients, specimens, and apparatus, which are used for following the progress of patients, for teaching, and for illustrating contributions to medical literature. A filing system allows quick collection of previously completed illustrations of a large variety of subjects. The Out-Patient Departments, the Diagnostic Clinic, and the Maternity Department have profited particularly from the work of the Institute in the ability that it provides to reconstruct early conditions.

Lankenau Hospital.

The Research Division of the Institute, as is now generally known, has concerned itself with the problem of the chemistry of cell growth, and its researches in the subject of sulphur metabolism have directed attention from many quarters to the work of the Institute and the Hospital of which it is a part.

Presbyterian Hospital. The Presbyterian Hospital, incorporated in 1871, and opened the following year, was a happy product of the reunion, in 1869, of the two branches of the Presbyterian Church.

This Hospital, which never has had any restrictions as to race, creed, or color, has a consulting and major staff of about 170, and provides beds for 425 patients. The Out-Patient Department, with an annual visit-total of about 63,000, offers clinics in allergy, diseases of the heart, diabetes, thy-

roid and other conditions. A Child Health Clinic follows the Department for Prevention of Disease of the Children's Hospital, in emphasizing the modern doctrine of prevention.

The physicians and interns, as in most hospitals, hold weekly clinical conferences in the laboratory for the discussion of unusual pathological conditions which arise in the routine of observation in the Hospital, and papers and other presentations are delivered at monthly scientific meetings. Recently a research committee has been instituted with a view to extending the general importance of the work done in the Hospital.

Presbyterian Hospital.

In general, coöperation between the Hospitals and the Medical Schools, at which we have hinted in speaking of the Graduate School of Medicine's "Pennsylvania Plan," is engaged in widely, and there can be little doubt that its ultimate effect is an advantageous one for all concerned.

It is to be expected that a city so rich in medical institutions should be rich alike in medical societies. About 50 of these announce their meetings in the Weekly Roster published by the Philadelphia County Medical Society, and these do not constitute the entire list. Two medical organizations must be mentioned especially. The largest in the city is the Philadelphia County Medical Society, at Twenty-First and Spruce Streets. Organized in 1849 under the presidency of Dr. Samuel Jackson, it has been from the beginning

an extraordinarily active and effective medical police in the interests of the public welfare. Of late years it has become increasingly active in stimulating the interest of the younger physicians, the interns and medical students, by series of postgraduate seminars and round table discussions held in its building. The Weekly Roster which it publishes is an invaluable guide to the activities of the city's medical societies.

U. S. Naval Hospital.

The oldest existing medical society in Philadelphia, and the most famous, is the College of Physicians, organized in 1787. Its present splendid home, which was built for it and to which it moved in 1909, houses one of the finest medical libraries in the world, both in size and quality. Its collections of medical incunabula and other medical books of the greatest rarity are known in Europe as well as in this country. Over 200 of the incunabula have already been photostated by the Library's photostatic machine and are accessible to scholars in the reading room.* These collections and one of the most comprehensive files of medical periodicals in the country have resulted in making the College a court of first resource for those working in medical literature. The College holds monthly scientific meetings, except during the summer, often with distinguished guest speakers, and its Fellows have organized five Sections which likewise hold monthly meetings in the lecture halls of the College, which are used also by other medical societies in the city. The College, thus, is open six full days and many evenings in the week, carrying on that "diffusion of medical knowledge" proposed as among its objects by one of its distinguished founders, Benjamin Rush.

*A special exhibit of some of the rarest items has been arranged for the American College of Physicians and, likewise, arrangements have been made to introduce its members to the Mutter Museum and other treasures in the College building.

Philadelphia's medical activities today include, further, the publication of 19 medical journals. Philadelphia is the home of five of the largest medical publishing houses in the country. Here the headquarters of the American College of Physicians was established in 1926. Philadelphia today teaches

Headquarters, The American College of Physicians, 4200 Pine Street.

medicine, practices medicine, thinks in terms of medical progress with the singular devotion which it inherits and passes on year by year. It is, in a spiritual sense at least, the medical center of America.

COLLEGE NEWS NOTES

New Life Members

The following Fellows of the College have become Life Members. (Listed in the order of subscription. Subscriptions received up to and including March 14, 1946.)

Dr. Kenelm Winslow Benson, Berkeley, Calif.
Dr. Paul Veal Ledbetter, Houston, Tex.
Dr. Henry Nathan Leopold, San Antonio, Tex.
Dr. Frank Reid Mount, Portland, Ore.
Dr. Henry Rohnert Carstens, Detroit, Mich.
Dr. J. Sudler Hood, Clearwater, Fla.
Dr. Archie Marvin Roberts, Los Angeles, Calif.
Dr. Eugene Fagan Traut, Oak Park, Ill.
Dr. Kenneth S. Davis, Los Angeles, Calif.
Dr. Oscar Benwood Hunter, Washington, D. C.
Dr. James Burnett Shields, Glens Falls, N. Y.
Dr. Earl Charles Waterbury, Newburgh, N. Y.
Dr. Lorenz William Frank, Denver, Colo.
Dr. Harold Lazarus Tonkin, Williamsport, Pa.
Dr. William Sullivan Horn, Fort Worth, Tex.
Dr. William Campbell Blake, Tampa, Fla.
Dr. Lawrence Chatfield Towne, Lansing, Mich.
Dr. William R. Vis, Grand Rapids, Mich.
Dr. William Crane Nichols, Fargo, N. D.
Dr. Henry Costill Gotshalk, Honolulu, T. H.

All Governors of the College Have Returned from Military Service

During the period of the war several Governors of the College were on active duty with the Medical Corps of the Army and the Navy. We are gratified to report that all have returned to their home states and have now resumed their posts as Governors of the College.

Tribute should be made to those Fellows who accepted the responsibility of Acting Governors during the absence of the regular Governors. Each one performed with enthusiasm and efficiency the duties of Governor and was largely responsible for the maintenance of College activities and College interests in his respective state.

Dr. Thomas M. McMillan was the Acting Governor for Eastern Pennsylvania during the absence of Dr. Edward L. Bortz; Dr. Patrick L. Ledwidge, Detroit, was the Acting Governor for Michigan in the absence of Dr. Douglas Donald; Dr. Edward H. Rynearson, Rochester, was the Acting Governor for Minnesota during the absence of Dr. Edgar V. Allen; Dr. Ellsworth L. Amidon, Burlington, was the Acting Governor for Vermont during the absence of Dr. Paul K. French; Dr. Edwin G. Bannick, Seattle, was the Acting Governor for Washington during the absence of Dr. Charles E. Watts; Dr. Richard Hawkes, Portland, was the Acting Governor for Maine during the absence of Dr. Eugene H. Drake.

Dr. Wetherbee Fort was for a time Acting Governor for Maryland during the absence of Dr. Louis Krause, and Dr. J. Edwin Wood, Jr., was the Acting Governor

for Virginia during the absence of Dr. Walter B. Martin, but there was one election held during the war when Drs. Fort and Wood were officially elected Governors for their respective states and Dr. Walter B. Martin was elected a member of the Board of Regents.

COURSE NO. 9—A.C.P. POSTGRADUATE PROGRAM—SPRING 1946—THORACIC DISEASES.

Owing to unavoidable circumstances, Dr. John Alexander, Professor of Surgery at the University of Michigan Medical School will be unable to assume the directorship of Course No. 9—Thoracic Diseases, scheduled to be given at Ann Arbor from May 6–11, 1946. Dr. Alexander's assistant, Dr. Cameron Haight, Associate Professor of Surgery, University of Michigan Medical School has agreed to direct this course for the American College of Physicians.

We regret very much that Dr. Alexander has been forced to withdraw, but we are confident that Dr. Haight will direct this course as ably as would Dr. Alexander. The subject matter remains the same and the schedule has already been announced in the Final Bulletin of Postgraduate Courses for the Spring (page 34). The Thoracic Surgery Staff of the University Hospital and other members of the University of Michigan Medical School Faculty are prepared to carry on in Dr. Alexander's absence. Registration for this course is now open and should be made directly with the College Headquarters Office in Philadelphia.

COURSE NO. 5—A.C.P. POSTGRADUATE PROGRAM—SPRING 1946—NUTRITION.

An intensive, personalized course in "Nutrition and Nutritional Deficiency States" will be directed by Dr. Tom D. Spies at the Nutrition Clinic of the Hillman Hospital in Birmingham, Alabama, for a small group of from 10 to 15 men, beginning June 3 and ending June 8. This course was first announced in the College News Notes in the February number of the Annals of Internal Medicine and has been included in our Final Bulletin of Spring Courses.

The course will be devoted to the various phases of nutrition and nutritional deficiencies in a practical and stimulating manner, including clinics and ward rounds, field studies, and laboratory demonstrations. Deficiency producting diets and therapeutic diets will be stressed. The principles of nutrition and metabolism will be defined, and the diagnosis and treatment of deficiency states will be presented by means of informal discussions and clinics. Nutrition in relation to dentistry, heart failure, and public health will be noted.

Registration is now open and will be limited to a maximum of 15 men. Reservations will be made in the order of their receipt at College Headquarters in Philadelphia. Hotel accommodations will be provided through the courtesy of the Birmingham Chamber of Commerce.

Dr. Edward de S. Matthews, F.A.C.P., New Orleans, recently retired from the Army and has resumed the practice of internal medicine and cardiology at New Orleans, being associated with Dr. Chaille Jamison, Clinical Professor of Medicine, Emeritus, at Tulane University. Dr. Matthews holds an appointment as Instructor in Medicine at Tulane.

Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, has recently been honored by the Director General of the Republic

of El Salvador, Central America, for proficient scientific work in the field of public health. Dr. Geiger was awarded an honorary degree granting him the title of "Benemerito de la Salubridad Continental."

Dr. Wann Langston, F.A.C.P., Oklahoma City, Professor of Medicine and Chairman of the Department of Medicine, has been appointed Temporary Dean of the University of Oklahoma School of Medicine.

Dr. Currier McEwen, F.A.C.P., has returned from military service with the rank of Colonel and with the Bronze Star and the Legion of Merit, and has resumed his duties as Dean of the New York University College of Medicine. In July 1945, Col. McEwen became Chief Consultant in Medicine for the European Theater of Operations with Headquarters in Paris and Frankfurt.

Dr. Robert P. McCombs, F.A.C.P., formerly of Philadelphia, has recently been separated from the Navy and has assumed the position of Director of the Postgraduate Division and Assistant Professor of Medicine, Tufts College Medical School, with offices at the Joseph H. Pratt Diagnostic Hospital, Boston.

Dr. Ernest E. Irons, F.A.C.P., Chicago, Ill., President of the American College of Physicians and member of the Board of Trustees of the American Medical Association, recently attended a testimonial dinner in Nashville in honor of Dr. Harrison H. Shoulders, President-Elect of the American Medical Association.

Dr. Wallace M. Yater, F.A.C.P., Washington, has been appointed Associate Editor of the *American Heart Journal*.

Dr. William H. Leake, F.A.C.P., Beverly Hills, Calif., was named President of the Medical Veterans Organization in that region.

Col. James O. Gillespie, F.A.C.P., MC, USA, was first reported "missing in action" in the early part of the war. He had been stationed in the Philippines at the time of the final surrender at Corregidor. Later information coming through in 1943 informed us that he was a prisoner of the Japanese. Col. Gillespie was liberated after the fall of Japan and has returned to the United States, his address being, 3444 Divisadero Street, San Francisco, California.

Capt. John F. McManus, MC, AUS, F.A.C.P., was recently made Chief of Medical Service at the U. S. Army General Hospital, Camp Edwards, Mass. It is anticipated that he may soon be released from active duty and will then return to the practice of internal medicine in Boston.

Dr. George C. Griffith, F.A.C.P., formerly of Philadelphia, after separation from the Naval Reserve, has opened an office at 117 E. Colorado Street, Pasadena, California, for practice limited to consultation in Cardiovascular Disease.

Dr. Henry S. Houghton, F.A.C.P., who preceding the war was Acting Director of the Peiping Union Medical College, Peiping, China, was held as a political prisoner by the Japanese for the duration of the war, having been released shortly after the middle of August 1945. He returned to this country and is now restored in health and strength. His headquarters is with the Trustees of the Peiping Union Medical College, 49 W. 49th Street, New York City.

Dr. George N. Barry, F.A.C.P., Oklahoma City, Oklahoma, has been serving in the U. S. Naval Reserve since June 13, 1945, but has not previously been recorded in these columns on active duty. This brings the total number of members of the College serving with the Army, Navy, or Public Health Service to 1982.

Brigadier General William C. Menninger, F.A.C.P., Director of the Neuropsychiatry Consultants Division, Office of The Surgeon General, has been awarded the Distinguished Service Medal for "solving one of the most serious medical problems faced by the Army" in activating a plan of treatment for neuropsychiatric cases, which restored many thousands of mentally sick men to health and usefulness.

Lt. Col. Philip T. Knies, MC, F.A.C.P., Army Quarantine Liaison Officer, Preventive Medicine Service, Office of The Surgeon General, has received the Legion of Merit for his work in the "planning, organization, and supervision of the Army foreign quarantine program."

Dr. F. M. Pottenger, F.A.C.P., Monrovia, California, was recently given signal honor by the Los Angeles County Tuberculosis and Health Association, which presented him with a handsome parchment scroll commending his outstanding leadership in the fight against Tuberculosis. Dr. Pottenger has been elected President Emeritus with "voice and vote on the Board of Directors," of the Los Angeles County Tuberculosis and Health Association.

The late Dr. Philip H. Pierson, F.A.C.P., has been honored posthumously by the Board of Trustees of the Alum Rock Sanatorium, San Jose, California, who dedicated a gift of $5000 to a Memorial Medical Research Fund in honor of our former distinguished Fellow. Dr. Pierson, formerly Clinical Professor of Medicine at Stanford University Medical School and consultant at Alum Rock Sanatorium, died unexpectedly on January 17, 1946.

Dr. Harold G. Trimble, F.A.C.P., is Chairman of the Board of Trustees and Dr. B. H. Wardrip, F.A.C.P., is Secretary of the Board of Trustees of Alum Rock Sanatorium.

For the past month Tulane University of Louisiana School of Medicine, Department of Graduate Medicine, has been conducting review courses in various phases of general medical practice. The program from the middle of April until the end of May is as follows:

April 15–20, Diseases of Nervous System
April 22–27, Nutritional and Metabolic Diseases
April 29–May 4, Infectious Diseases
May 6–11, Neoplastic Diseases
May 13–18, Obstetrics and Gynecology
May 20–25, Traumatology

Dr. E. David Sherman, F.A.C.P., Sydney, Nova Scotia, has been appointed Consultant in Medicine to the Department of Veterans Affairs Hospital.

The Division of Medical Services of the School District of Philadelphia has sponsored a symposium on The Heart and The School Child. The following Fellows of the College, who reside in the city of Philadelphia, took part in this program:

Jacob M. Cahan, M.D., F.A.C.P.
Alexander Margolies, M.D., F.A.C.P.
Charles C. Wolferth, M.D., F.A.C.P.
Ella Roberts, M.D., F.A.C.P.
Mary H. Easby, M.D., F.A.C.P.
Geo. Howard Gehrmann, M.D., F.A.C.P.
Samuel Bellet, M.D., F.A.C.P.
Carl C. Fischer, M.D., F.A.C.P.

Lt. E. A. Rasberry, Jr., (MC), USN, has been awarded a Clinical Fellowship in Medicine to begin on or about July 1, 1946. Dr. Rasberry will serve this Fellowship at the Hospital of the University of Pennsylvania, Philadelphia, under the directorship of Dr. T. Grier Miller in the Department of Gastro-enterology.

Dr. Robert P. Morehead, F.A.C.P., Winston-Salem, N. C., who is Associate Professor of Pathology and Director of that department at the Bowman Gray School of Medicine of Wake Forest College, has been appointed Educational Director of the North Carolina Division of the field army of the American Cancer Society.

Gifts To The College Library

The following gifts of publications by members are gratefully acknowledged:

Irene V. Allen (Associate), New Brunswick, Can.—1 reprint.
Joseph L. Hollander (Associate), Hot Springs National Park, Ark.—1 reprint.
Victor H. Kugel (Associate), Cambridge, Ohio—2 reprints.
B. Oliver Lewis, F.A.C.P., Galveston, Tex.—2 reprints.
George X. Schwemlein (Associate), Chicago, Ill.—2 reprints.
Norman R. Shulack (Associate), Brooklyn, N. Y.—2 reprints.

The Council Committee on Public Health and Education of the Medical Society of the State of New York is sponsoring courses of instruction in Pulmonary Diseases and Tuberculosis under the auspices of the New York State Department of Health. These courses will be given at Hermann M. Biggs Memorial Hospital, Ithaca, N. Y., Homer Folks Tuberculosis Hospital, Oneonta, N. Y., Mount Morris Tuberculosis Hospital, Mount Morris, N. Y., New York State Hospital, Ray Brook, N. Y., and are designed primarily for medical officers returning from service with the Armed Forces. Each State Tuberculosis Hospital has arranged to accommodate four residents for a minimum period of instruction of three months or a maximum of twelve months. This training will provide a basic background for a career in sanatorium work, public health, or later specialization in thoracic diseases. The plan is endorsed by the medical

schools in Albany, Buffalo, Rochester, and Syracuse, as well as by the United States Public Health Service which has allocated funds to provide a reasonable monthly stipend, if certain qualifications can be met by applicants. Inquiries should be addressed to Robert E. Plunkett, M.D., General Superintendent of Tuberculosis Hospitals, New York State Department of Health, Alfred E. Smith State Office Building, Albany 1, New York.

The next written examination of the American Board of Internal Medicine will be held on October 21. The closing date for the acceptance of applications is July 1. There are no written examinations in the sub-specialties:

Allergy
Cardiovascular Disease
Gastro-enterology
Tuberculosis

The School of Medicine of the College of Medical Evangelists, Los Angeles, California, has developed it's graduate teaching program along four lines:

Residency
Fellowship
Precepteeship
Graduate Courses

Preparation for Specialty Board examination is stressed. Further information may be obtained from the Dean, W. F. Norwood, M.D., Los Angeles Division, College of Medical Evangelists, White Memorial Hospital, Boyle & Michigan Avenues, Los Angeles 35, California.

Northwestern University, Evanston, Ill., plans to develop its Chicago campus to meet the vastly increased need for research in medicine, dentistry, law, business, government, and aeronautics. The new program will require from $95,000,000 to $150,000,000 to erect in Chicago 16 new buildings, and provide a large endowment for research and teaching. It is estimated that from 20 to 25 years will be required to put this plan in complete operation.

Among the various objectives included in this campus plan of Northwestern University, top listing has been given to the development of a great medical center that will place major emphasis on medical research. Ten new buildings are envisaged which, together with the necessary equipment and endowment will require a sum ranging from $63,000,000 to $95,000,000. It is believed that this proposed development, in time, will make Chicago the world's greatest center for medical teaching and research, according to Dr. James Roscoe Miller, F.A.C.P., Dean of Northwestern's Medical School.

The faculty of Columbia University College of Physicians and Surgeons has established residencies and fellowships to provide training in physical medicine on a graduate level. Applications should be submitted to the directors of the following hospitals:

Presbyterian Hospital, 620 West 168th Street, New York 32.
New York Post-Graduate Medical School and Hospital, 303 East 20th Street, New York 3.

Mount Sinai Hospital, Fifth Avenue at 100th Street, New York 29.
St. Luke's Hospital, 421 West 113th Street, New York 25.
Goldwater Memorial Hospital, Welfare Island, New York.
Montefiore Hospital, 150 East Gunhill Road, New York 67.
Hospital for Joint Diseases, 1919 Madison Avenue, New York 35.

The Michigan State Medical Society and the medical schools of the University of Michigan, Ann Arbor, and Wayne University, Detroit, are coöperating in a course on medical economics. Details of the course may be obtained from the Dean's office at each university.

The Norton Medical Award of $3500 which is offered by W. W. Norton & Company, Inc. of 70 Fifth Avenue, New York 11, N. Y., to encourage the writing of books on medicine and the medical profession for the layman, is now open for competition. Terms of the Award and publication may be obtained from the Publishers. The Award is offered for a book to be published in 1947. Announcement will be made shortly of the winning book for 1946. Closing date for submission of manuscripts this current year is November 1.

Examinations for appointments of medical officers in the Regular Corps of the United States Public Health Service are now under way at various convenient localities throughout the country. Examinations will be oral and written. The written examination will be held on May 14, 15 and 16 at places convenient to the candidate and the Service. The oral examination will begin at 9:00 a.m. at the places and dates listed below:

Atlanta, Georgia—Malaria Control in War Areas, 605 Volunteer Bldg. . .	Apr. 22
Baltimore, Maryland—Marine Hospital, Wyman Park Drive & 31st Street	May 9
Boston, Massachusetts—Marine Hospital, 77 Warren Street (Brighton)	May 6
Chicago, Illinois—Marine Hospital, 4141 Clarendon Avenue	Apr. 30
	May 1
Cleveland, Ohio—Marine Hospital, Fairhill Road & E. 124th Street	May 3
Denver, Colorado—617 Colorado Bldg.	Apr. 8
Detroit, Michigan—Marine Hospital, Windmill Pointe	May 2
Fort Worth, Texas—U. S. Public Health Service Hospital	Apr. 25
Kirkwood, Missouri—near St. Louis—Marine Hospital, 525 Couch Ave. .	Apr. 26, 27
Los Angeles, California—USPHS Relief Station, 406 Federal Building .	Apr. 9
Minneapolis, Minn.—Office of Indian Affairs, 218 Federal Office Bldg. . .	Apr. 29
New Orleans, Louisiana—Marine Hospital, 210 State Street	Apr. 23, 24
New York, New York—Marine Hospital, Stapleton, Staten Island	May 7, 8
Norfolk, Virginia—Marine Hospital, Hampton Blvd., Larchmont	May 10
San Francisco, California—Marine Hospital, 14th Ave. & Park Blvd. . . .	Apr. 10, 11
Seattle, Washington—Marine Hospital, Judkins St. & 14th Ave. South .	Apr. 12, 13
Washington, D. C.—USPHS Dispensary, Fourth and D Streets SW. . . .	Apr. 4
	May 13

Application forms may be obtained by writing to the Surgeon General, U. S. Public Health Service, Washington 25, D. C.

The University of Rochester School of Medicine and Dentistry is sponsoring two programs for the benefit of returning veteran medical officers. The first is a Residency-Fellowship Program designed to qualify veteran physicians as specialists. This has been made possible by the creation of additional positions in the usual clinical fields and by increase in the number of Fellowships in the basic medical sciences.

To meet the needs of returning medical officers who desire a general review of the whole field of medicine, a Postgraduate Refresher Course has been established, which will run for a period of six weeks and cover the entire field of medicine and surgery and the specialties in a general way. Registration will be limited to a maximum of 30 men, and the course may be repeated if there is sufficient demand. Letters of application should be addressed to the Dean's Office, School of Medicine and Dentistry, 260 Crittenden Boulevard, Rochester 7, New York.

A National Society for Medical Research is being organized to protect animal experimentation in biology, dentistry, pharmacy and veterinary medicine from the inroads of political interference. Plans for this new society were sponsored by the Council on Medical Education and Hospitals of the American Medical Association and the Federation of State Medical Boards. The functions of the National Society for Medical Research shall be:

1. Education of the public relative to the necessity, importance, humane character and accomplishments of animal experimentation in medicine and biology.
2. Aid in preventing the enactment of national and local legislation restrictive to animal experimentation.
3. Promotion of legislation providing for the protection of animal experimentation in medicine and biology.

Under the auspicies of the Association of American Medical Colleges an organizing board of directors has been selected. Dr. A. J. Carlson, F.A.C.P. (University of Chicago) Chairman, Dr. Andrew C. Ivy, F.A.C.P. (Northwestern University) Secretary and Dr. C. Sidney Burwell, F.A.C.P. (Harvard Medical School) Chairman of the Executive Committee.

Professional and physical examinations for the Medical Corps, U. S. Navy, will be conducted at various naval hospitals from May 6–10. Successful candidates will be appointed as Assistant Surgeon and Acting Assistant Surgeon with the rank of Lieutenant (junior grade). Application forms and other data may be obtained by writing to the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C.

Retirements from Service

Since the last publication of this journal, the following members of the College have been reported retired or on terminal leave (to March 13, 1946 inclusive):

F. Dennette Adams, Boston, Mass. (Col., MC, AUS)
Ruel L. Alden, Hempstead, N. Y. (Major, MC, AUS)
Edward L. Alexander, Newport News, Va. (Comdr., MC, USNR)

Crawford N. Baganz, Lyons, N. J. (Lt. Comdr., MC, USNR)
John L. Baube, Mt. Vernon, Ohio (Major, MC, AUS)
James R. Bell, Cleveland, Ohio (Lt. Col., MC, AUS)

William O. Benenson, Napanoch, N. Y. (Lt. Col., MC, AUS)
Z. Taylor Bercovitz, New York, N. Y. (Lt. Col., MC, AUS)
Earl J. Bieri, Hot Springs, Ark. (Capt., MC, AUS)
Louis F. Bishop, Jr., New York, N. Y. (Lt. Col., MC, AUS)
Everett O. Black, Fredonia, N. Y. (Major, MC, AUS)
Morris Block, New York, N. Y. (Comdr., MC, USNR)
Allen G. Brailey, Brookline, Mass. (Lt. Comdr., MC, USNR)
Ward W. Briggs, Baltimore, Md. (Comdr., MC, USNR)
Leon Bromberg, St. Louis, Mo. (Capt., MC, USNR)
Frederick S. Bruckman, San Francisco, Calif. (Major, MC, AUS)
Burdette J. Buck, Hartford, Conn. (Lt. Col., MC, AUS)
Aaron L. Burger, Brooklyn, N. Y. (Lt. Col., MC, AUS)
George G. Burkley, Pittsburgh, Pa. (Lt. Comdr., MC, USNR)
William C. Buschemeyer, Louisville, Ky. (Capt., MC, AUS)

Mortimer J. Cantor, Brooklyn, N. Y. (Major, MC, AUS)
A. Albert Carabelli, Trenton, N. J. (Lt. Col., MC, AUS)
H. Dumont Clark, Denver, Colo. (Lt. Col., MC, AUS)
Howard C. Coggeshall, Dallas, Tex. (Major, MC, AUS)
William E. Costolow, Los Angeles, Calif. (Capt., MC, USNR)
P. Thurman Crawford, Memphis, Tenn. (Lt. Comdr., MC, USNR)
Hatch W. Cummings, Jr., Houston, Tex. (Comdr., MC, USNR)

John S. Davis, Jr., New York, N. Y. (Lt. Col., MC, AUS)
E. Rankin Denny, Tulsa, Okla. (Col., MC, AUS)
Mark S. Dougherty, Jr., Atlanta, Ga. (Lt. Comdr., MC, USNR)
Eugene H. Drake, Portland, Maine (Capt., MC, USNR)
Edgar Durbin, Denver, Colo. (Lt. Col., MC, AUS)

Frederick A. Eigenbrod, New Orleans, La. (Major, MC, AUS)
Earl B. Erskine, Jamaica, L. I., N. Y. (Comdr., MC, USN)
Peter Everett, III, New Orleans, La. (Capt., MC, AUS)
Harold K. Eynon, Collingswood, N. J. (Lt. Col., MC, AUS)

John L. Ferry, Akron, Ind. (Major, MC, AUS)
David Fertig, Hartsdale, N. Y. (Lt., MC, USNR)
Luther I. Fisher, Bethlehem, Pa. (Comdr., MC, USNR)
Ralph L. Fitts, Grand Rapids, Mich. (Capt., MC, AUS)
Hiland L. Flowers, New York, N. Y. (Lt. Col., MC, AUS)
Thomas F. Frist, Nashville, Tenn. (Major, MC, AUS)

Daniel M. Green, Jacksonville, Fla. (Lt. Col., MC, AUS)
Edward B. Grossman, New York, N. Y. (Major, MC, AUS)

Frederic W. Hall, Winfield, Kan. (Capt., MC, AUS)
Reid R. Heffner, New Rochelle, N. Y. (Major, MC, AUS)
Francis J. Heringhaus, Mansfield, Ohio, (Lt. Col., MC, AUS)
Iredell M. Hinnant, Cleveland, Ohio (Lt. Col., MC, AUS)
Samuel J. Hoffman, Chicago, Ill. (Lt. Col., MC, AUS)
Lyman H. Hoyt, Boston, Mass. (Comdr., MC, USNR)
Hyman M. Hurevitz, Davenport, Iowa (Major, MC, AUS)

Cullen W. Irish, Los Angeles, Calif. (Lt. Col., MC, AUS)

William A. Jeffers, Philadelphia, Pa. (Major, MC, AUS)
Hartwell Joiner, Gainesville, Ga. (Major, MC, AUS)
Benjamin Juliar, Detroit, Mich. (Capt., MC, AUS)

Boyd G. King, Cleveland, Ohio (Lt. Col., MC, AUS)
Robert C. Kirk, Columbus, Ohio (Major, MC, AUS)
Gerald Klatskin, New Haven, Conn. (Major, MC, AUS)
Phillip T. Knies, Columbus, Ohio (Col., MC, AUS)
Israel Kopp, Roxbury, Mass. (Capt., MC, AUS)
Philip Krainin, New York, N. Y. (Lt. Comdr., MC, USNR)

John J. Maisel, Buffalo, N. Y. (Major, MC, AUS)
Tim J. Manson, Chattanooga, Tenn. (Capt., MC, AUS)
Walter B. Martin, Norfolk, Va. (Col., MC, AUS)
Jesse McCall, Newton, N. J. (Lt. Col., MC, AUS)
Robert P. McCombs, Philadelphia, Pa. (Lt., MC, USNR)
Francis E. McDonough, Boston, Mass. (Lt. Col., MC, AUS)
Currier McEwen, New York, N. Y. (Lt. Col., MC, AUS)
John B. McKee, Winchester, Va. (Lt. Col., MC, AUS)
Theodore H. Mendell, Philadelphia, Pa. (Lt. Col., MC, AUS)
Joseph Mignone, New Haven, Conn. (Lt., MC, USNR)
Samuel Millman, Brooklyn, N. Y. (Lt. Col., MC, AUS)
Charles S. Mills, Phoenix, Ariz. (Major, MC, AUS)
Robert G. Murphy, Providence, R. I. (Capt., MC, AUS)

Robert J. Needles, St. Petersburg, Fla. (Lt. Col., MC, AUS)
Arthur D. Nichol, Cleveland, Ohio (Lt. Col., MC, AUS)
John Noll, Jr., Youngstown, Ohio (Lt. Col., MC, AUS)

Maurice C. Pincoffs, Baltimore, Md. (Col., MC, AUS)
Ross J. Porritt, Pontiac, Mich. (Major, MC, AUS)
John M. Porter, Concordia, Kan. (Comdr., MC, USNR)
Robert T. Porter, Greeley, Colo. (Major, MC, AUS)

Richard Z. Query, Jr., Charlotte, N. C. (Major, MC, AUS)

William O. Ramey, Cincinnati, Ohio (Capt., MC, USNR)
Jack O. W. Rash, Miami, Fla. (Major, MC, AUS)
Joseph W. Rastetter, Milwaukee, Wis. (Comdr., MC, USNR)
E. Burkett Reed, Lincoln, Nebr. (Capt., MC, AUS)
William D. Reid, Kezar Falls, Maine (Lt. Comdr., MC, USNR)
Anthony E. Reymont, Santa Fe, N. M. (Capt., MC, USNR)
Edwin L. Rippy, Dallas, Tex. (Lt. Col., MC, AUS)
Abraham I. Rosenstein, New York, N. Y. (Capt., MC, AUS)
Henry C. Rosenstiel, Freeport, Ill. (Major, MC, AUS)
Thomas L. Ross, Jr., Macon, Ga. (Major, MC, AUS)
Maurice J. Rotkow, Des Moines, Iowa (Capt., MC, AUS)
Chauncey L. Royster, Raleigh, N. C. (Major, MC, AUS)
J. Griswold Ruth, Benton Harbor, Mich., (Capt., MC AUS)

S. Marion Salley, Miami, Fla. (Lt. Col., MC, AUS)
John B. Schwedel, New York, N. Y. (Comdr., MC, USNR)

Euclid M. Smith, Hot Springs, Ark. (Lt. Col., MC, AUS)
Raymond A. Sokolov, Detroit, Mich. (P. A. Surgeon, USPHS (R))
Robert F. Solley, New York, N. Y. (Comdr., MC, USNR)
Irving E. Steck, Chicago, Ill. (Major, MC, AUS)
Charles W. Steele, Lewiston, Maine (Lt. Col., MC, AUS)
Stuart Dos Passos Sunday, Baltimore, Md. (Lt. Col., MC, AUS)

Myer Teitelbaum, Detroit, Mich. (Capt., MC, AUS)
Kent H. Thayer, Phoenix, Ariz. (Major, MC, AUS)
Charles E. Thompson, Omaha, Nebr. (Major, MC, AUS)
Kilby P. Turrentine, Kinston, N. C. (Lt. Comdr., MC, USNR)

Lee D. van Antwerp, Meriden, Conn. (Major, MC, AUS)
Raymond G. Vinal, Norwell, Mass. (Major, MC, AUS)

Levi M. Walker, Atlantic City, N. J. (Major, MC, AUS)
Harry A. Warren, Champaign, Ill. (Lt. Col., MC, AUS)
Oliver W. Welch, Fairfield, Ala. (Capt., MC, AUS)
Martin H. Wendkos, Philadelphia, Pa. (Major, MC, AUS)
William G. Weston, Arkansas City, Kan. (Major, MC, AUS)
Clarence B. Whims, Ventnor City, N. J. (Major, MC, AUS)
Asher A. White, Minneapolis, Minn. (Major, MC, AUS)
Duncan Whitehead, Utica, N. Y. (Lt. Col., MC, AUS)
Arthur T. Wyatt, Lillington, N. C. (Lt. Col., MC, AUS)

Richard H. Young, Evanston, Ill. (Lt. Col., MC, AUS)

1945 Operations

THE AMERICAN COLLEGE OF PHYSICIANS

The accounts of the American College of Physicians, ending December 31, 1945, have been audited by a Public Accountant, and the following statements are printed for the information of members. The net increase in the Endowment Fund was $26,453.45 and in the General Fund, $16,592.56, increasing these Funds to $196,196.84 $225,278.44, respectively; total assets of the College, December 31, 1945, $421,475.28.

Balance Sheet

General Fund

Current Assets:			
Cash in Bank and on Hand		$ 51,072.73	
Accounts Receivable		5,738.81	
Loans Receivable		1,500.00	
Inventory of Keys, Pledges & Frames		364.05	
Accrued Income, General Fund Investments	$ 528.55		
Accrued Income, Endowment Fund investments	1,202.48	1,731.03	
Investments, at Book Value		$126,454.79	
Insurance Deposit		555.00	$187,416.41

Fixed Assets:

College Headquarters, Real Estate	$57,728.45		
Less: Reserve for Depreciation	9,000.00	48,728.45	
Investment, Real Estate, 404–12 S. 42nd St.		9,170.50	
Furniture & Equipment	12,322.98		
Less: Depreciation	9,525.07	2,797.91	60,696.86
Gross Assets, General Fund			$248,113.27

Liabilities:

Current:

Accounts Payable	$ 1,170.32		
Chicago Postgraduate Fund	713.30	1,883.62	

Deferred Income:

Subscriptions to the "Annals of Internal Medicine," paid in advance	17,974.47		
Advertising in "Annals of Internal Medicine," paid in advance	692.44	18,666.91	

Reserve:

Philadelphia Postgraduate Fund		2,284.30	
Total Liabilities		$ 22,834.83	
General Fund		225,278.44	$248,113.27

SUMMARY OF OPERATIONS, General Fund

Year Ending December 31, 1945

Income:

Annual Dues			23,684.67	
Initiation Fees			9,815.00	
Subscriptions, "Annals of Internal Medicine"			42,723.96	
Advertising, "Annals of Internal Medicine"			14,706.98	
Income from Investments, General Fund			5,564.80	
Income from Investments, Endowment Fund			5,795.64	
Dividends on Perpetual Insurance Deposit			60.00	
Keys, Pledges and Frames			17.54	
1943 Membership Roster			1.50	
Rent, 404–12 S. 42nd St.		$ 1,620.00		
Less: Maintenance	$322.87			
Water Tax	14.96			
Real Estate Taxes	489.55	827.38	792.62	
Profit from Sale of Securities (General Fund)			1,684.64	
TOTAL				$104,847.35

Expenditures:

Salaries		28,513.23	
Postage, Telephone and Telegraph		3,983.27	
Office Supplies and Stationery		1,489.78	
Printing		25,876.82	
Traveling Expenses		2,939.55	
Miscellaneous Expenses		1,667.07	
College Headquarters:			
Maintenance	$ 2,037.99		
Heat, Light, Gas & Water	780.05		
Taxes	170.77		
Insurance	72.22	3,061.03	
Depreciation on Building	$ 1,000.00		
Depreciation on Furniture & Equipment	833.99	1,833.99	
Investment Counsel & Custodian Fees		527.53	
Regional Meetings		1,566.43	
Postgraduate Courses, 1945		1,939.68	
War-Time Graduate Medical Meetings		5,000.00	
Collection & Exchange		26.53	
Loss on Sale or Maturity of Investments, General Fund		159.62	
1945 Membership Roster		188.28	
1945 Annual Meeting		15.08	
Pension Fund		3,481.90	82,269.79
Net Income Year 1945			$ 22,577.56

General Fund

Balance, January 1, 1945	208,685.88	
Less: Transfer to Endowment Fund of Initiation Fees of Life Members	5,985.00	202,700.88
		$225,278.44

BALANCE SHEET

Endowment Fund

Current Assets:

Cash in Bank	$ 22,163.61	
Accrued Income	1,202.48	
Investments	174,033.23	$197,399.32
Endowment Fund Principal	196,196.84	
Accrued Income Due General Fund	1,202.48	$197,399.32

Endowment Fund Operation

Endowment Fund Principal, January 1, 1945		$169,743.39
Add:		
Life Membership Fees Received during 1945	$ 17,500.00	
Transfer of Initiation Fees of Life Members from General Fund	5,985.00	
Net Gain from Sale of Endowment Fund Investments	2,968.45	26,453.45
Endowment Fund		$196,196.84

OBITUARIES

DR. FRANK HERBERT BARTLETT, JR.

Dr. Frank Herbert Bartlett, Jr. F.A.C.P., was born in Lynn, Mass., July 25, 1894. After receiving his early education in the Lynn English High School, he entered Tufts Medical College from which he was graduated in 1919. Soon after graduation, he was appointed Assistant Director of the Central Maine Sanitarium in Westfield, Maine. From there he went to Healthwinn, the St. Joseph County Tuberculosis Sanitarium, South Bend, Indiana. In 1923, he became Director of the Livingstone County Tuberculosis Hospital at Pontiac, Illinois. On December 6, 1926, he became Director of the Muskegon County Tuberculosis Sanitarium, Muskegon, Michigan, and continued in that capacity until his death.

He was a Trustee of the Michigan Tuberculosis Society, a member of the American Trudeau Society, a Fellow of the American College of Physicians, a member of the Mississippi Valley Conference on Tuberculosis, and the National Tuberculosis Association. He was a past president of the Muskegon County Medical Society, a thirty-second degree Mason and a member of the B. P. O. Elks, Rotary Club, and the Alpha Kappa Kappa Medical Fraternity.

Dr. Bartlett was deeply interested in his specialty and during his time as Director of the Muskegon County Tuberculosis Sanitarium, the death rate from tuberculosis in Muskegon County decreased 74 per cent.

He died January 25, 1946, from a fractured skull, resulting from a fall down the basement stairs at his home.

WILLIAM M. LEFEVRE, M.D., F.A.C.P.

DR. GEORGE EMANUEL HOLTZAPPLE

George Emanuel Holtzapple, M.D., Sc.D. (Hon.), F.A.C.P., York, Pennsylvania, died at his home on Washington's Birthday, February 22, at the age of eighty-three years and nine months. He was born in West Manchester Township, York County, May 22, 1862, where he attended the public school for a grand total of fifty-five months—most of his early education having been obtained at his country home by the flicker of a candlestick. He later attended the York Collegiate Institute and York County Academy, walking four and a half miles morning and evening, and living on a lunch that cost three to five cents! He began his study of medicine at the Baltimore Medical College, later transferring to Bellevue Medical College, New York, where he was graduated in 1884. He later did postgraduate work at the New York Postgraduate Medical School, Johns Hopkins Medical School, and in various clinics throughout the country. Dr. Holtzapple was ever interested in keeping in close touch with the latest developments in medi-

cine, and attended the Annual Sessions of the College with great regularity. He also took some of its postgraduate courses up until the age of eighty.

Dr. Holtzapple was attending physician, and later consulting physician and chief of the Neuropsychiatric Clinic, York Hospital, and for a period of five years was President of the Staff. He was a Member, and Past President of the York County Medical Society; Member, Medical Society of the State of Pennsylvania (one-time Chairman of the Medical Section); American Medical Association; American College of Physicians (1920). He was also a Diplomate of the American Board of Internal Medicine (1937).

Among his outstanding achievements were his pioneer work in the administration of oxygen for the relief of anoxemia in pneumonia, and his brilliant observations in a large group of Family Periodic Paralysis.

Dr. Holtzapple was also deeply interested in civic and religious affairs in his community and held many posts of honor and trust in its various important activities, being at one time President of the School Board of York.

He was a fine and cultured gentleman, of high moral character, and a distinguished clinician. His professional attainments were of the very highest order, and he was truly a profound student, and a clinician of excellent judgment. His loss will be very keenly felt by the medical profession and the community he served so well and long.

Dr. Holtzapple is survived by his widow and three children.

JULIUS H. COMROE, M.D., F.A.C.P.

DR. NEWTON GURDON EVANS

Dr. Newton Gurdon Evans, B.S., F.A.C.P., of South Pasadena, died December 19, 1945 at the White Memorial Hospital, Los Angeles, of carcinoma, at the age of seventy-one.

Dr. Evans was born at Hamilton, Missouri, June 1, 1874. He attended Battle Creek College, later transferring to Union College, from which he received his B.S degree in 1895. He then entered the American Medical Missionary College, later transferring to Cornell University Medical College, receiving his M.D. degree in 1900. He studied post graduate at the University of Chicago, Cornell University and the Mayo Foundation. During 1900–1905 he was Instructor in Histology, American Medical Missionary College; Professor of Pathology, 1908–1911, University of Tennessee College of Medicine; Professor of Pathology, Vice President of the faculty, later becoming President, College of Medical Evangelists, Los Angeles. He was Chairman of the Board of the Alumni Research Foundation, College of Medical Evangelists; Pathologist and Secretary of the Malignancy Board, Los Angeles County Hospital; Lieutenant Colonel (inactive) of the Medical Reserve Corps, U. S. Army. He was former President of the Los Angeles Pathological Society, Los Angeles Cancer Society, American Association of

Pathologists and Bacteriologists; member of the American Society of Clinical Pathologists, Los Angeles Academy of Medicine, California State Medical Association and American Association for the Advancement of Science. He was a Fellow of the American Medical Association, and The American College of Physicians, the latter since 1921, and a Counselor of the Surgeon General's Library.

In early 1945 his portrait was presented to the White Memorial Library.

ROY E. THOMAS, M.D., F.A.C.P.,
Governor for Southern California

DR. CHARLES T. WAY

Dr. Charles T. Way, F.A.C.P., was born near Taylor, North Dakota, in 1887. He attended Beloit College, Wisconsin, graduating with a B.S. degree in 1914. After three years of teaching, he turned to medicine and attended Western Reserve University School of Medicine graduating in 1921. Following an internship and residency at Saint Luke's Hospital, Cleveland, Ohio, he began the practice of medicine and was closely associated with Saint Luke's Hospital until ill health forced his resignation from the position of Director of Medicine. Dr. Way was an enthusiastic and able teacher. He held the positions, successively, of Instructor, Senior Instructor, and Assistant Clinical Professor of Medicine at his Alma Mater. He was always interested in organized medicine and took an active part in the Cleveland Academy of Medicine, serving for a number of years on its Board of Directors and was its President from 1940–1941. His industry, open, friendly personality, and ability not only brought him recognition in his profession but a host of devoted friends. He was an ardent hunter and lover of the out-of-doors, and an enthusiastic member of the Canadian Camp Fire Club. He died on February 4, 1946, from arteriolar nephrosclerosis and uremia, a disease to which he had devoted a considerable portion of his research capacity and to the knowledge of which he had made numerous scientific contributions.

JOSEPH M. HAYMAN, JR., M.D., F.A.C.P.

DR. ARCHIBALD D. SMITH

Archibald D. Smith, M.D., F.A.C.P., Garden City, New York, died at the Brooklyn Hospital, November 22, 1945, of coronary thrombosis. Dr. Smith was born in 1876, received his A.B. degree in 1898 from Yale University and his M.D. degree in 1902 from Columbia University College of Physicians and Surgeons. For many years he was Pediatrician at the

Brooklyn Hospital, and thereafter Consulting Pediatrician at that institution and at the Rockaway Beach Hospital and Dispensary.

Dr. Smith was a former president of the Brooklyn Academy of Pediatrics and the Brooklyn Pediatric Society; a member of the American Academy of Pediatrics. He had been head of a civilian defense medical unit in Garden City during World War II.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York